Clinical trial results:
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)

Summary

EudraCT number	2015-004632-35
Trial protocol	DE
Global end of trial date	25 November 2019

Results information

Result version number	v1
This version publication date	02 October 2020
First version publication date	02 October 2020

Trial information

Trial identification

Sponsor protocol code	CLCZ696BDE01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02768298
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.
Regarding rescue medication, patients received open-label angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) during the study ONLY if the study medication was discontinued either temporarily or permanently. A 36 hours washout phase of study drug was needed before start of an ACEI.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 201
Worldwide total number of subjects	201
EEA total number of subjects	201

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	77
From 65 to 84 years	118
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Participants took part in 34 investigative sites in Germany.

Pre-assignment

Screening details:

Participants were randomized 1:1 to receive either LCZ696 or enalapril during the double-blind period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696

Arm description:

LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.

Arm type	Experimental
Investigational medicinal product name	Sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks

Arm title	Enalapril

Arm description:

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.

Arm type	Active comparator
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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 subjects in period 1	LCZ696	Enalapril
Started	103	98
Completed	99	91
Not completed	4	7
Adverse event, serious fatal	2	1
Adverse event, non-fatal	1	4
Non-compliance with study treatment	-	1
Withdrawal of informed consent	-	1
Subject/guardian decision	1	-

Baseline characteristics

Reporting groups	
Reporting group title	LCZ696
Reporting group description:	
LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	
Reporting group title	Enalapril
Reporting group description:	
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.	

Reporting group values	LCZ696	Enalapril	Total
Number of subjects	103	98	201
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	43	34	77
From 65-84 years	57	61	118
85 years and over	3	3	6
Age Continuous Units: Years			
arithmetic mean	66.1	67.6	
standard deviation	± 10.792	± 9.961	-
Sex: Female, Male Units: Participants			
Female	17	21	38
Male	86	77	163
Race/Ethnicity, Customized Units: Subjects			
Caucassian	101	96	197
Black	0	1	1
Other	2	1	3

End points

End points reporting groups

Reporting group title	LCZ696
Reporting group description:	
LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	
Reporting group title	Enalapril
Reporting group description:	
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.	

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

End point title	Change from baseline in peak respiratory oxygen uptake (VO2peak) adjusted to body weight) after 3 months of treatment
End point description:	
Cardiopulmonary exercise testing (CPET) is an established method to evaluate the exercise tolerance of heart failure patients by evaluating the cardio-pulmonary system using the measurement of respiratory gases during physical (exercise) stress. One of the parameters attained by this test is the peak respiratory oxygen uptake (VO2peak). CPET to assess VO2peak was performed at a cycle ergometer at baseline (Visit 2, 9 days prior randomization) and after 6 weeks and 3 months of treatment (Visit 6 and Visit 7, respectively). The VO2peak adjusted to body weight was calculated based on the corresponding visit's VO2peak (unadjusted) and body weight data by using the following formula: VO2peak (unadjusted)/body weight. Higher values of VO2peak indicate less symptom severity and therefore a positive change from baseline indicates improvement.	
End point type	Primary
End point timeframe:	
Baseline, 3 months	

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	90		
Units: mL/kg/min				
least squares mean (standard error)	0.51 (± 0.180)	0.19 (± 0.188)		

Statistical analyses

Statistical analysis title	VO2peak- 3 months
Comparison groups	LCZ696 v Enalapril

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2327
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.85
Variability estimate	Standard error of the mean
Dispersion value	0.268

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

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

End point description:

Cardiopulmonary exercise testing (CPET) is an established method to evaluate the exercise tolerance of heart failure patients by evaluating the cardio-pulmonary system using the measurement of respiratory gases during physical (exercise) stress. One of the parameters attained by this test is the peak respiratory oxygen uptake (VO2peak).
CPET to assess VO2peak was performed at a cycle ergometer at baseline (Visit 2, 9 days prior randomization) and after 6 weeks and 3 months of treatment (Visit 6 and Visit 7, respectively).
The VO2peak adjusted to body weight was calculated based on the corresponding visit's VO2peak (unadjusted) and body weight data by using the following formula: VO2peak (unadjusted)/body weight.
A positive change from baseline indicates less symptom severity.

End point type	Secondary

End point timeframe:

Baseline, 6 weeks

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	88		
Units: mL/kg/min				
least squares mean (standard error)	0.28 (± 0.185)	0.42 (± 0.195)		

Statistical analyses

Statistical analysis title	VO2peak
Comparison groups	LCZ696 v Enalapril

Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6247
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	0.277

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

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

End point description:

Cardiopulmonary exercise testing (CPET) is an established method to evaluate the exercise tolerance of heart failure patients by evaluating the cardio-pulmonary system using the measurement of respiratory gases during physical (exercise) stress. One of the parameters attained by this test is the minute ventilation (VE) to carbon dioxide output slope (VE/VCO2 slope). High values of VE/VCO2 slope resembles the inability to eliminate CO2 by respiration (inefficient ventilation).
A negative change from baseline indicates less symptom severity.

End point type	Secondary

End point timeframe:

Baseline, 6 weeks, 3 months

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	98		
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 analyses

Statistical analysis title	VE/VCO2 slope

Statistical analysis description:

6 weeks

Comparison groups	LCZ696 v Enalapril

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1678
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	0.52
Variability estimate	Standard error of the mean
Dispersion value	0.888

Statistical analysis title	VE/VCO2 slope
Statistical analysis description:	
3 months	
Comparison groups	LCZ696 v Enalapril
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3052
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	2.43
Variability estimate	Standard error of the mean
Dispersion value	0.809

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

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

End point description:

Cardiopulmonary exercise testing (CPET) is an established method to evaluate the exercise tolerance of heart failure patients by evaluating the cardio-pulmonary system using the measurement of respiratory gases during physical (exercise) stress. CPET was performed at a cycle ergometer with a workload that started at 10 watts (W) and then increased by 10W for each 1-minute stage.
Exercise capacity assessed as workload in watts was determined at the ventilatory anaerobic threshold (VAT) which represents the transition from aerobic to partially anaerobic glucose metabolism in muscle, leading to increasing carbon dioxide exhalation in comparison to oxygen uptake.
A positive change from baseline in exercise capacity (watt) indicates improvement.

End point type	Secondary

End point timeframe:
Baseline, 6 weeks, 3 months

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	98		
Units: Watt				
least squares mean (standard error)				
6 weeks 3 months	1.71 (± 1.168) 2.45 (± 1.436)	0.83 (± 1.234) -0.83 (± 1.483)		

Statistical analyses

Statistical analysis title	Ventilatory anaerobic threshold
Statistical analysis description: 6 weeks	
Comparison groups	LCZ696 v Enalapril
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6181
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.58
upper limit	4.32
Variability estimate	Standard error of the mean
Dispersion value	1.744

Statistical analysis title	Ventilatory anaerobic threshold
Statistical analysis description: 3 months	
Comparison groups	LCZ696 v Enalapril
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1254
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	3.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	7.48
Variability estimate	Standard error of the mean
Dispersion value	2.124

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

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

End point description:

The individually perceived exertion, in terms of perceived dyspnea and perceived fatigue, during cardiopulmonary exercise testing (CPET) was assessed by Borg scale which is a 15 point scale, starting from 6 which indicates "No exertion at all" to 20 which means "Maximal exertion".
Change in Borg scale for both perceived dyspnea and perceived fatigue were measured at different time points at Baseline (Visit 2, 9 days prior randomization) and 3 months of treatment (Visit 7). Maximum value among the time points at every visit was used for the analysis.
A negative change from baseline in Borg value of perceived dyspnea and perceived fatigue indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, 3 months

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	98		
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 analyses

Statistical analysis title	Borg value dyspnea
Comparison groups	LCZ696 v Enalapril
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3432
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.317

Statistical analysis title	Borg value fatigue
Comparison groups	LCZ696 v Enalapril
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5319
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.251

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days (16 weeks on average).	
Adverse event reporting additional description:	
Any signs or symptoms that occurs during study treatment plus the 30 days post treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	LCZ696
Reporting group description:	
LCZ696	
Reporting group title	Enalapril
Reporting group description:	
Enalapril	

Serious adverse events	LCZ696	Enalapril	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 103 (11.65%)	14 / 98 (14.29%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Angiocardiogram			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio abnormal			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 103 (1.94%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			

subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 103 (0.97%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 103 (1.94%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			

subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 103 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent occlusion			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 103 (0.97%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 103 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 103 (1.94%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 103 (0.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LCZ696	Enalapril	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 103 (50.49%)	36 / 98 (36.73%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	27 / 103 (26.21%)	11 / 98 (11.22%)	
occurrences (all)	29	11	
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 103 (13.59%)	6 / 98 (6.12%)	
occurrences (all)	14	6	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	2 / 103 (1.94%)	7 / 98 (7.14%)	
occurrences (all)	2	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 103 (2.91%)	9 / 98 (9.18%)	
occurrences (all)	3	9	
Dyspnoea			
subjects affected / exposed	2 / 103 (1.94%)	6 / 98 (6.12%)	
occurrences (all)	2	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 103 (8.74%)	3 / 98 (3.06%)	
occurrences (all)	10	3	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	9 / 103 (8.74%)	3 / 98 (3.06%)	
occurrences (all)	10	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2016	The section "Other concomitant treatment – ACEIs and ARBs – was reworded to clearly state that both ACEI and ARB were prohibited during treatment with double-blind study medication. If ACEI and/or ARB were initiated, study medication had to be discontinued. It was clarified that 36 hour wash-out period was necessary for ACEI, but not for ARB.
05 December 2017	Eligibility was adapted to clarify two exclusion criteria: planned heart transplant or ventricular assistance device (VAD) during the expected study duration of 14 weeks, and diagnosed long QT syndrome. It was explicitly stated in section "Other concomitant medication" that concomitant heart failure medication should be stable 4 weeks prior to screening Visit 1 and until randomization Visit 3.
21 January 2019	The primary packaging of enalapril 5 mg and 10 mg tablets was updated.
24 July 2019	The term "lean body weight" was changed to "body weight" throughout the protocol and therefore the primary (adjusted VO2peak after 3 months of treatment) and secondary endpoint (adjusted VO2peak after 6 weeks of treatment) were changed. RER=1 was exchanged to ventilatory anaerobic threshold (VAT) for the secondary endpoint "Exercise capacity (Watt)".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported