Clinical trial results:
A randomized, double-blind, active-controlled study to assess the effect of sacubitril/valsartan compared with enalapril to improve erectile function in patients with heart failure with reduced ejection fraction (HFrEF) and erectile dystunction (ED)

Summary

EudraCT number	2018-000220-33
Trial protocol	DE
Global end of trial date	25 May 2021

Results information

Result version number	v1 (current)
This version publication date	04 June 2022
First version publication date	04 June 2022

Trial information

Trial identification

Sponsor protocol code	CLCZ696BDE03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03917459
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Dislcosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 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 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 May 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate the superiority of sacubitril/valsartan compared to enalapril regarding improvement in erectile function and ability in male patients with chronic heart failure and erectile dysfunction using the International Index of Erectile Function (IIEF-15) questionnaire at the end of the study.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	10
From 65 to 84 years	17

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirteen patients were randomized to the LCZ696 group, 14 were randomized to the Enalapril group. Twelve patients in the LCZ696 group and 13 patients in the enalapril group completed the study. One patient from the LCZ696 group discontinued due to Adverse Event. One patient from the enalapril group discontinued due to subject decision.

Pre-assignment

Screening details:

Thirteen patients were randomized to the LCZ696 group, 14 were randomized to the Enalapril group. Twelve patients in the LCZ696 group and 13 patients in the enalapril group completed the study. One patient from the LCZ696 group discontinued due to Adverse Event. One patient from the enalapril group discontinued due to subject decision.

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	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696

Arm description:

LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg bid)

Arm type	Experimental
Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

LCZ696 200 mg

Investigational medicinal product name	Placebo to match sacubitril/valsartan
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg

Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

LCZ696 100 mg

Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Film-coated tablet

Routes of administration	Oral use
Dosage and administration details: LCZ696 50 mg	
Investigational medicinal product name	Placebo to match sacubitril/valsartan
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 100 mg	
Investigational medicinal product name	Placebo to match sacubitril/valsartan
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 50 mg	
Arm title	Enalapril
Arm description: 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 10 mg	
Investigational medicinal product name	Placebo to match Enalapril
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg	
Investigational medicinal product name	Placebo to match Enalapril
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 2.5 mg	
Investigational medicinal product name	Placebo to match Enalapril
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 5 mg	

Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Enalapril 2.5 mg

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

Number of subjects in period 1	LCZ696	Enalapril
Started	13	14
Completed	12	13
Not completed	1	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	LCZ696
Reporting group description:	
LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg bid)	
Reporting group title	Enalapril
Reporting group description:	
Enalapril 10 mg bid	

Reporting group values	LCZ696	Enalapril	Total
Number of subjects	13	14	27
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)	7	3	10
From 65-84 years	6	11	17
85 years and over	0	0	0
Age Continuous			
Units: Count of Participants			
arithmetic mean	63.5	66.5	
standard deviation	± 9.18	± 7.80	-
Sex: Female, Male			
Gender			
Units: Participants			
Female	0	0	0
Male	13	14	27
Race (NIH/OMB)			
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	13	14	27
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups	
Reporting group title	LCZ696
Reporting group description: LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg bid)	
Reporting group title	Enalapril
Reporting group description: Enalapril 10 mg bid	

Primary: Erectile function score using Index of Erectile Function (IIEF-15)	
End point title	Erectile function score using Index of Erectile Function (IIEF-15)
End point description: The International Index of Erectile Function (IIEF-15) was used to assess erectile function score in male patients with chronic heart failure. IIEF-15 is a patient self-reported assessment of erectile dysfunction (ED) and consists of 15 questions assessing five main principles associated with ED: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. For erectile function score, questions 1-5 and 15 were evaluated and summed. For each question, 0-5 points could be achieved with 5 being the highest score assigned, which corresponded to the most favorable outcome.	
End point type	Primary
End point timeframe: Week 12 (3 months)	

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: Percentage score				
least squares mean (standard error)	15.1 (± 2.15)	12.2 (± 2.00)		

Statistical analyses

Statistical analysis title	LCZ696 vs Enalapril
Comparison groups	LCZ696 v Enalapril
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3432
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	LS mean of treatment difference
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.29
upper limit	9.01

Secondary: Summary of change from baseline in Self-reported frequency of sexual activity per week

End point title	Summary of change from baseline in Self-reported frequency of sexual activity per week

End point description:

Assessment of early-onset effect and end of study effect, regarding improvement in sexual activity, using patient's self-reported frequency of sexual activity per week. Patient was asked to complete a diary assessing sexual activity on a weekly basis

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 12

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: Number				
arithmetic mean (standard deviation)				
Week 4:	-1.6 (± 1.59)	-1.1 (± 1.97)		
Week 12:	-1.4 (± 3.13)	-2.0 (± 3.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of change from baseline in NT-proBNP levels

End point title	Summary of change from baseline in NT-proBNP levels

End point description:

Change in n-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels compared to baseline assessed at Week 4 and Week 12

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 12

End point values	LCZ696	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: pg/mL				
median (full range (min-max))				
Week 4	-369.0 (-4884.0 to 1590.0)	-43.50 (-198.0 to 7819.0)		
Week 12	-208.50 (-6962.0 to 2683.0)	-189.00 (-826.0 to 1744.0)		

Statistical analyses

No statistical analyses for this end point

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 post treatment, up to a maximum duration of approximately 2 years, 1 month.

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus the 30 days post treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Enalapril

Reporting group description:

Enalapril

Reporting group title	LCZ696

Reporting group description:

LCZ696

Serious adverse events	Enalapril	LCZ696	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (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	Enalapril	LCZ696	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)	7 / 13 (53.85%)	
Investigations			
Blood potassium decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gout			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2019	The classification of the clinical phase of the trial was adjusted. In addition, exclusion criterion 33 was modified and the end of the study was defined in more detail.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was early terminated on 25-May-2021. 27 patients were randomized instead of planned 200 patients. The reason for preliminary study stop was recruitment issues. There were no safety issues in the study.

Notes: