Clinical trial results:
A multi-center, randomized, placebo-controlled patient and investigator-blinded study to explore the efficacy of oral sacubitril/valsartan in adult patients with non-obstructive hypertrophic cardiomyopathy (nHCM)

Summary

EudraCT number	2019-003098-24
Trial protocol	DE ES GB FI GR
Global end of trial date	22 August 2023

Results information

Result version number	v1 (current)
This version publication date	23 August 2024
First version publication date	23 August 2024

Trial information

Trial identification

Sponsor protocol code	CLCZ696I12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04164732
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure 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	22 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of LCZ696 on cardiopulmonary exercise test (CPET) parameters in patients with nHCM.

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	08 January 2020
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: 7
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	46
EEA total number of subjects	32

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)	32
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Germany (4 sites), Greece (2 sites), Korea (2 sites), Spain (4 sites), United Kingdom (1 site), United States (5 sites)

Pre-assignment

Screening details:

Patients who met eligibility criteria entered a single-blind treatment run-in period. Patients who were unable to tolerate either placebo or the 50 mg p.o. b.i.d. dose level,were considered treatment run-in failures and were not randomized into the double-blind, placebo-controlled study

Period 1

Period 1 title	Treatment run-in period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-in (All Participants)

Arm description:

All patients received oral (p.o.) placebo b.i.d. for 2 weeks, followed by 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks

Arm type	experimental and placebo
Investigational medicinal product name	placebo and LCZ696
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

all patients received oral (p.o.) placebo b.i.d. for 2 weeks followed by 50 mg p.o. of active LCZ696 b.i.d. for 2 weeks.

Number of subjects in period 1	Run-in (All Participants)
Started	46
Completed	40
Not completed	6
Physician decision	1
Screen Failure	1
Adverse event, non-fatal	4

Period 2

Period 2 title	Randomized treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696 BID

Arm description:

Patients were treated with LCZ696. The target dose level was 200 mg p.o. b.i.d.

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

Dosage and administration details:

Participants started at a LCZ696 100 mgp.o. b.i.d dose. After approximately 14days, patients who tolerated the 100 mgp.o. b.i.d. dose were up-titrated to 200mg p.o. b.i.d. dose, whereas those whodid not meet the safety criteria weretitrated back down to the 50 mg b.i.d.dose

Arm title	Placebo BID

Arm description:

Placebo to LCZ696

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

Dosage and administration details:

Placebo to LCZ696

Number of subjects in period 2	LCZ696 BID	Placebo BID
Started	20	20
Randomized analysis set	20	20
Per protocol analysis set	19	19
Completed	17	19
Not completed	3	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Protocol Deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment run-in period

Reporting group description: -

Reporting group values	Treatment run-in period	Total	
Number of subjects	46	46	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	14	14	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	55.7		
standard deviation	± 13.42	-	
Sex: Female, Male Units: Participants			
Female	12	12	
Male	34	34	
Race/Ethnicity, Customized Units: Subjects			
Asian	6	6	
White	40	40	

End points

End points reporting groups

Reporting group title	Run-in (All Participants)
Reporting group description:	
All patients received oral (p.o.) placebo b.i.d. for 2 weeks, followed by 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks	
Reporting group title	LCZ696 BID
Reporting group description:	
Patients were treated with LCZ696. The target dose level was 200 mg p.o. b.i.d.	
Reporting group title	Placebo BID
Reporting group description:	
Placebo to LCZ696	

Primary: Change from baseline in peak VO2 as measured by cardiopulmonary exercise test (CPET)

End point title	Change from baseline in peak VO2 as measured by cardiopulmonary exercise test (CPET)
End point description:	
The primary analysis assessed the effect of LCZ696 on the change from baseline in peak Volume of Oxygen (VO2) (ml/kg/min) at week 50 compared to placebo, where baseline peak VO2 came from the screening/baseline CPET. An increase in peak VO2 (mL/kg/min)/positive change is considered beneficial for the patient.	
End point type	Primary
End point timeframe:	
Baseline to 50 weeks	

End point values	LCZ696 BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: mL/kg/min				
least squares mean (confidence interval 90%)	1.00 (-0.22 to 2.23)	0.39 (-0.80 to 1.58)		

Statistical analyses

Statistical analysis title	model-based arithmetic mean estimates
Comparison groups	LCZ696 BID v Placebo BID
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5506
Method	longitudinal mixed effects (MMRM) model
Parameter estimate	Median difference (net)
Point estimate	0.61

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.71
upper limit	1.94

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 54 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Run-In Period Placebo
Reporting group description:	
Run-In Period Placebo	
Reporting group title	Double-blind period placebo
Reporting group description:	
Double-blind period placebo	
Reporting group title	Total
Reporting group description:	
Total	
Reporting group title	Double-blind period LCZ696 100 mg
Reporting group description:	
Double-blind period LCZ696 100 mg	
Reporting group title	Double-blind period LCZ696 200 mg
Reporting group description:	
Double-blind period LCZ696 200 mg	
Reporting group title	Double-blind period LCZ696
Reporting group description:	
Double-blind period LCZ696	
Reporting group title	Run-In LCZ696 50 mg
Reporting group description:	
Run-In LCZ696 50 mg	
Reporting group title	Double-blind period LCZ696 50 mg
Reporting group description:	
Double-blind period LCZ696 50 mg	

Serious adverse events	Run-In Period Placebo	Double-blind period placebo	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	3 / 46 (6.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Bundle branch block left			

subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block right			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-blind period LCZ696 100 mg	Double-blind period LCZ696 200 mg	Double-blind period LCZ696
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	2 / 17 (11.76%)	3 / 20 (15.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block right			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Run-In LCZ696 50 mg	Double-blind period LCZ696 50 mg	
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4.99 %

Non-serious adverse events	Run-In Period Placebo	Double-blind period placebo	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 46 (8.70%)	10 / 20 (50.00%)	26 / 46 (56.52%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 20 (5.00%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Asthenia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Sleep apnoea syndrome			
subjects affected / exposed	0 / 46 (0.00%)	1 / 20 (5.00%)	2 / 46 (4.35%)
occurrences (all)	0	1	2
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Foreign body in eye			
subjects affected / exposed	0 / 46 (0.00%)	1 / 20 (5.00%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 46 (4.35%)	1 / 20 (5.00%)	5 / 46 (10.87%)
occurrences (all)	2	1	5
Syncope			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	2
Tension headache			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 46 (2.17%)	0 / 20 (0.00%)	2 / 46 (4.35%)
occurrences (all)	1	0	2
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Gastric disorder			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Diarrhoea			

subjects affected / exposed	1 / 46 (2.17%)	0 / 20 (0.00%)	3 / 46 (6.52%)
occurrences (all)	1	0	3
Abdominal pain upper			
subjects affected / exposed	0 / 46 (0.00%)	2 / 20 (10.00%)	2 / 46 (4.35%)
occurrences (all)	0	2	2
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Nocturia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 20 (0.00%)	2 / 46 (4.35%)
occurrences (all)	1	0	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 46 (0.00%)	1 / 20 (5.00%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Diarrhoea infectious			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 20 (5.00%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
COVID-19			
subjects affected / exposed	0 / 46 (0.00%)	5 / 20 (25.00%)	5 / 46 (10.87%)
occurrences (all)	0	5	5

Diverticulitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	0 / 46 (0.00%)	0 / 20 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	0 / 46 (0.00%)	1 / 20 (5.00%)	1 / 46 (2.17%)
occurrences (all)	0	1	1

Non-serious adverse events	Double-blind period LCZ696 100 mg	Double-blind period LCZ696 200 mg	Double-blind period LCZ696
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	7 / 17 (41.18%)	12 / 20 (60.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	2 / 17 (11.76%)	3 / 20 (15.00%)
occurrences (all)	0	2	3
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Sleep apnoea syndrome			

subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Foreign body in eye			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	2 / 17 (11.76%)	2 / 20 (10.00%)
occurrences (all)	0	2	2
Syncope			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	2	2
Tension headache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Gastrointestinal sounds abnormal			

subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Gastric disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Nocturia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Diarrhoea infectious			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1

Cystitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Gout			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Run-In LCZ696 50 mg	Double-blind period LCZ696 50 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 43 (9.30%)	1 / 1 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 43 (2.33%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Foreign body in eye			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Syncope			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Tension headache			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 43 (2.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastric disorder			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nocturia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Diarrhoea infectious			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Cystitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
COVID-19			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Diverticulitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gout			
subjects affected / exposed	0 / 43 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2020	• Protocol summary - Key inclusion and exclusion criteria were corrected to reflect the criteria listed in Section 5 of the protocol. • Section 3 Study design - Clarified the use of safety criteria to assess tolerability of study medication. • Section 4.2 Rationale for selection of patient population - Added rationale for the NT-proBNP cutoff required to screen asymptomatic patients. • Section 4.7 Risks and benefits - Clarified risk of fetal harm by study medication if women of childbearing potential become pregnant while on study medication. • Section 5.1 Inclusion criteria - Inclusion criteria 4 has been updated to allow asymptomatic/NYHA Class I patients with peak VO2 of 80% to enroll in the study to harmonize with exclusion criteria 4. • Section 5.2 Exclusion criteria - Exclusion criteria 3 was clarified to exclude only those patients with a history of atrial fibrillation within 6 months of the screening/baseline visit. • Section 8 Visit schedule and assessments - Corrected a typographical error to make clear the requirement for recording adverse events during the screening/baseline period. • Section 8.4.4 Laboratory evaluations - Added clarification that plasma samples instead of serum samples can be collected for local laboratory analysis as per local practice. • Section 10.2.1 Liver safety monitoring - Correction made to indicate that results of local liver chemistry tests associated with a liver event should be recorded in source documents rather than in the CRF. • Section 12.7 Interim Analysis - Added clarification that the planned interim analysis will also include review of safety data.
01 April 2022	• Section 2 Objectives and Endpoints - Added information in Table 2.1 (Objectives and related endpoints) about collection of NYHA as an exploratory endpoint. • Section 5.1 Inclusion criteria - Added additional text to emphasize to sites that Informed Consent must be signed prior to discontinuation of ACE-I/ARB during the >36 hour washout period, if applicable. • Section 8 Visit schedule and assessments - Added the specific time points in Table 8.1 for data collection of NYHA class information at screening/baseline and Week 50 or EOS (if the patient discontinues the study prior to the Week 50 assessment). - Added Table 8.2 NYHA functional class table with standard descriptions of each functional class • Section 10.1.3 SAE reporting - Added additional text for clarification on investigator reporting timelines for SAEs

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported