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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Sacubitril/Valsartan

Trial Indication(s)

Hypertrophic cardiomyopathy

Protocol Number

CLCZ696I12201

Protocol Title

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)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Full development

Study Start/End Dates

Study Start Date: January 08, 2020 (Actual)

Primary Completion Date: August 22, 2023 (Actual)
Study Completion Date: August 22, 2023 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, placebo-controlled, patient and investigator-blinded study in non-obstructive HCM patients.

The study comprised a ≤ 35-day screening/baseline period, a 4-week single-blind treatment run-in period, followed by a 46-week double-blind placebo-controlled treatment period (total treatment period of 50 weeks), and a follow-up period approximately 30 days after the last dose.

The treatment run-in period was planned to ensure that as large a proportion as possible of patients:

(1) had stable symptoms and could comply with study visits, and

(2) could tolerate at least low dose LCZ696.

During the run-in period, 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. 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 neither randomized into the double-blind, placebo-controlled study, nor included in the efficacy analysis.

In the double-blind treatment period, participants were randomized 1:1 to placebo or LCZ696. In the LCZ696 arm, participants started at a LCZ696 100 mg p.o. b.i.d dose. After approximately 14 days, patients who tolerated the 100 mg p.o. b.i.d. dose were up-titrated to 200 mg p.o. b.i.d. dose, whereas those who did not meet the safety criteria were titrated back down to the 50 mg b.i.d. dose.

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Centers

18 centers in 6 countries: United States(5), Germany(4), Spain(4), Korea, Republic of(2), Greece(2), United Kingdom(1)

Objectives:

Primary objective

• To evaluate the effect of LCZ696 on cardiopulmonary exercise test (CPET) parameters in patients with non-obstructive hypertrophic cardiomyopathy (nHCM).

Secondary objective

• To evaluate the safety and tolerability of LCZ696 in patients with nHCM.

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

- Oral tablet of LCZ696 50 mg or matching placebo
- Oral tablet of LCZ696 100 mg or matching placebo
- Oral tablet of LCZ696 200 mg or matching placebo

Statistical Methods

The safety analysis set included all patients that received any study drug.
The randomized analysis set (RAS) consisted of all randomized patients.
The per-protocol analysis set (PPS) is a subset of the RAS that consists of all randomized patients who have no major protocol deviations with relevant impact on PD/efficacy data, and who are at least 80% compliant with the overall study drug administration.

The primary analysis assessed the effect of LCZ696 on the change from baseline in peak VO_2 at week 50 compared to placebo in the PPS. A longitudinal mixed effects model for the change from baseline was used. The model included treatment, time (as a categorical variable), and the treatment-by-time interaction as fixed effects, patient as a random effect, and baseline peak VO_2 as a covariate. The least-squares (LS) mean and associated 90% confidence interval (CI) for the change from baseline in peak VO_2 for each treatment, and the estimated mean treatment difference, the p-value, and the corresponding 2-sided 80% CI was extracted from the model.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Diagnosed with Hypertrophic Cardiomyopathy with a left ventricular wall thickness greater than or equal to 13mm as determined by the echocardiogram obtained during the screening/baseline period
- Left ventricular ejection fraction (LVEF) greater than or equal to 50% as determined by echocardiogram obtained during the screening/baseline period
- Symptoms consistent with New York Heart Association (NYHA) Class II-III heart failure by physician assessment, or asymptomatic/NYHA Class I patients with:
-- NT-proBNP blood sample levels above 250 pg/ml and
-- peak VO2 of less than or equal to 80% of predicted based on age and gender as determined by cardiopulmonary exercise testing

Exclusion Criteria:

- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for ≥7 days after stopping study drug
- Patients with a resting or provokable left ventricular outflow tract gradient of greater than or equal to 30mm Hg
- Septal reduction procedure within 3 months of the screening/baseline visit
- History of atrial fibrillation within 6 months of the screening/baseline visit or placement of ICD for secondary prevention

- Patients with a peak VO2 on the screening/baseline cardiopulmonary exercise test of > 80% of predicted based on age and gender
- Patients who require treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), or renin inhibitors
- Known infiltrative or storage disorder such as Fabry disease, or amyloidosis
- Known or suspected symptomatic coronary artery diseases or evidence of prior myocardial infarction
- Systolic blood pressure of <100 mmHg or symptomatic hypotension during the screening/baseline period or treatment run-in period
- Contraindication to ARB administration or prior history of angioedema
- Persistent uncontrolled hypertension

Participant Flow Table

Treatment run-in period

	Run-in (All Participants)	LCZ696 BID	Placebo BID	Total
Arm/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	Patients were treated with LCZ696. The target dose level was 200 mg p.o. b.i.d.	Placebo to LCZ696	
Started	46	0	0	46
Completed	40	0	0	40
Not Completed	6	0	0	6
Adverse Event	4	0	0	4
Physician Decision	1	0	0	1
Screen Failure	1	0	0	1

Randomized treatment period

	Run-in (All Participants)	LCZ696 BID	Placebo BID	Total
Arm/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	Patients were treated with LCZ696. The target dose level was 200 mg p.o. b.i.d.	Placebo to LCZ696	
Started	0	20	20	40
Randomized analysis set	0	20	20	40
Per protocol analysis set	0	19	19	38
Completed	0	17	19	36
Not Completed	0	3	1	4
Adverse Event	0	1	0	1
Protocol Deviation	0	1	1	2
Withdrawal by Subject	0	1	0	1

Baseline Characteristics

	Run-in (All Participants)	LCZ696 BID	Placebo BID	Total
Arm/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	Patients were treated with LCZ696. The target dose level was 200 mg p.o. b.i.d.	Placebo to LCZ696	
Number of Participants [units: participants]	6	20	20	46
Baseline Analysis Population Description				
Age Continuous (units: years)				

Analysis Population Type: Participants Mean ± Standard Deviation				
	54.5±17.19	54.5±11.84	57.2±14.29	55.7±13.42
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	3	3	6	12
Male	3	17	14	34
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Asian	1	2	3	6
White	5	18	17	40

Primary Outcome Result(s)

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

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.
Time Frame	Baseline to 50 weeks
Analysis Population Description	Patients in the per protocol analysis set with and available value for the outcome measure at baseline and Week 50 . Per protocol analysis set consists of all randomized patients who had no major protocol deviations with relevant impact on PD/efficacy data and who are at least 80% compliant with the overall study drug administration.

	LCZ696 BID	**Placebo BID**

Arm/Group Description	Patients were treated with LCZ696. The target dose level was 200 mg p.o. b.i.d.	Placebo to LCZ696
Number of Participants Analyzed [units: participants]	18	19
Change from baseline in peak VO2 as measured by cardiopulmonary exercise test (CPET) (units: mL/kg/min)	**Least Squares Mean (90% Confidence Interval)**	**Least Squares Mean (90% Confidence Interval)**
	1.00 (-0.22 to 2.23)	0.39 (-0.80 to 1.58)

Statistical Analysis

Groups	LCZ696 BID, Placebo BID
Type of Statistical Test	Superiority
P Value	0.5506
Method	Other longitudinal mixed effects (MMRM) model
Median Difference (Net)	0.61
80 % Confidence Interval 2-Sided	-0.71 to 1.94

Secondary Outcome Result(s)

No data identified.

Other Pre-Specified Outcome Result(s)

No data identified.

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Post-Hoc Outcome Result(s)

Ratio of Week 50 to baseline peak VO2 as measured by cardiopulmonary exercise test (CPET)

Description	Descriptive analysis to support interpretation of primary analysis.
Time Frame	Baseline, week 50
Analysis Population Description	Patients in the per protocol analysis set with and available value for the outcome measure at baseline and Week 50 . Per protocol analysis set consists of all randomized patients who had no major protocol deviations with relevant impact on PD/efficacy data and who are at least 80% compliant with the overall study drug administration.

	LCZ696 BID	Placebo BID
Arm/Group Description	Patients were treated with LCZ696. The target dose level was 200 mg p.o. b.i.d.	Placebo to LCZ696
Number of Participants Analyzed [units: participants]	17	18
Ratio of Week 50 to baseline peak VO2 as measured by cardiopulmonary exercise test (CPET) (units: Ratio (Week 50 / Baseline))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	1.07 ± 0.166	1.05 ± 0.215

Safety Results

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (26.0)

Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Run-In Period Placebo N = 46	Run-In LCZ696 50 mg N = 43	Double-blind period placebo N = 20	Double-blind period LCZ696 50 mg N = 1	Double-blind period LCZ696 100 mg N = 20	Double-blind period LCZ696 200 mg N = 17	Double-blind period LCZ696 N = 20	Total N = 46
Arm/Group Description	All patients received oral (p.o.) placebo b.i.d. for 2 weeks	All patients received 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks	Patients in the double-blind period treated with placebo	Patients in the double-blind period treated with LCZ696 50mg	Patients in the double-blind period treated with LCZ696 100mg	Patients in the double-blind period treated with LCZ696 200mg	All patients in the double-blind period treated with LCZ696	Total
Total Number Affected	0	0	0	0	0	0	0	0
Total Number At Risk	46	43	20	1	20	17	20	46

Serious Adverse Events

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

	Run-In Period Placebo N = 46	Run-In LCZ696 50 mg N = 43	Double-blind period placebo N = 20	Double-blind period LCZ696 50 mg N = 1	Double-blind period LCZ696 100 mg N = 20	Double-blind period LCZ696 200 mg N = 17	Double-blind period LCZ696 N = 20	Total N = 46
Arm/Group Description	All patients received oral (p.o.) placebo b.i.d. for 2 weeks	All patients received 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks	Patients in the double-blind period treated with placebo	Patients in the double-blind period treated with LCZ696 50mg	Patients in the double-blind period treated with LCZ696 100mg	Patients in the double-blind period treated with LCZ696 200mg	All patients in the double-blind period treated with LCZ696	Total
Total # Affected by any Serious Adverse Event	0	0	0	0	1	2	3	3
Total # at Risk by any Serious Adverse Event	46	43	20	1	20	17	20	46
Cardiac disorders								
Atrioventricular block second degree	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Bundle branch block left	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Bundle branch block right	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Cardiac failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Coronary artery disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (2.17%)
Respiratory, thoracic and mediastinal disorders								
Chronic obstructive pulmonary disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)

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Other (Not Including Serious) Adverse Events

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	4.99%

	Run-In Period Placebo N = 46	**Run-In LCZ696 50 mg N = 43**	**Double-blind period placebo N = 20**	**Double-blind period LCZ696 50 mg N = 1**	**Double-blind period LCZ696 100 mg N = 20**	**Double-blind period LCZ696 200 mg N = 17**	**Double-blind period LCZ696 N = 20**	**Total N = 46**
Arm/Group Description	All patients received oral (p.o.) placebo b.i.d. for 2 weeks	All patients received 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks	Patients in the double-blind period treated with placebo	Patients in the double-blind period treated with LCZ696 50mg	Patients in the double-blind period treated with LCZ696 100mg	Patients in the double-blind period treated with LCZ696 200mg	All patients in the double-blind period treated with LCZ696	Total
Total # Affected by any Other Adverse Event	4	4	10	1	6	7	12	26

Total # at Risk by any Other Adverse Event	46	43	20	1	20	17	20	46
Blood and lymphatic system disorders								
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (2.17%)
Cardiac disorders								
Palpitations	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Ear and labyrinth disorders								
Vertigo	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (2.17%)
Gastrointestinal disorders								
Abdominal pain upper	0 (0.00%)	0 (0.00%)	2 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.35%)
Diarrhoea	1 (2.17%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	3 (6.52%)
Gastric disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Gastrointestinal sounds abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (2.17%)
Vomiting	1 (2.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	2 (4.35%)
General disorders and administration site conditions								
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Chest pain	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.17%)
Oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Infections and infestations								
COVID-19	0 (0.00%)	0 (0.00%)	5 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (10.87%)
Cystitis	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.17%)

Diarrhoea infectious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Diverticulitis	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.17%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Injury, poisoning and procedural complications								
Foreign body in eye	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.17%)
Investigations								
SARS-CoV-2 test positive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Metabolism and nutrition disorders								
Abnormal loss of weight	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (2.17%)
Gout	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.17%)
Musculoskeletal and connective tissue disorders								
Back pain	1 (2.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	2 (4.35%)
Nervous system disorders								
Dizziness	2 (4.35%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	2 (11.76%)	2 (10.00%)	5 (10.87%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Tension headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Renal and urinary disorders								
Nocturia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)

Renal impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Respiratory, thoracic and mediastinal disorders								
Chronic obstructive pulmonary disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (2.17%)
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (2.17%)
Sleep apnoea syndrome	0 (0.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	2 (4.35%)
Skin and subcutaneous tissue disorders								
Angioedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.88%)	1 (5.00%)	1 (2.17%)
Vascular disorders								
Hypotension	0 (0.00%)	1 (2.33%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	2 (11.76%)	3 (15.00%)	4 (8.70%)

Other Relevant Findings

Not applicable

Conclusion:

- Overall, oral sacubitril/valsartan was generally safe in the adult non-obstructive hypertrophic cardiomyopathy (nHCM) population with no observed unexpected or new safety findings.
- The safety profile observed was consistent with the current knowledge of the product safety profile.
- Notably, AEs suggest an acceptable tolerability and a manageable safety profile in this population.
- The clinical response was stable in most of the nHCM patients treated with oral sacubitril/valsartan, but there was no improvement in peak Volume of Oxygen (VO_2) (mL/kg/min) at Week 50.

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Date of Clinical Trial Report

05 June 2024