NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Sacubitril/valsartan (LCZ696)

Trial Indication(s)

Reduced ejection fraction (HFrEF) and Erectile dysfunction (ED)

Protocol Number

CLCZ696BDE03

Protocol Title

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 and erectile dysfunction

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3B

Study Start/End Dates

Study Start Date: April 2019 (Actual)
Primary Completion Date: May 2021 (Actual)
Study Completion Date: May 2021 (Actual)

Reason for Termination (If applicable)

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.

Study Design/Methodology

This study was a randomized, double-blind, double-dummy, multi-center, active-controlled interventional study to compare LCZ696 200 mg bid to enalapril 10 mg bid in improving erectile function in male patients with chronic heart failure (NYHA II) and reduced ejection fraction and erectile dysfunction.

Centers

Germany(13)

Objectives:

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

Secondary objectives were:

- To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding improvement in sexual activity assessed using patient's self-reported frequency of sexual activity per month

- To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding NT-proBNP levels

The study was preliminarily stopped due to low recruitment rate.

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

The following study medications were provided:

- LCZ696 50 mg, 100 mg, and 200 mg film-coated tablets
- Placebo to match LCZ696 50 mg, 100 mg, and 200 mg film-coated tablets
- Enalapril 2.5 mg, 5 mg, and 10 mg tablets
- Placebo to match enalapril 2.5 mg, 5 mg, and 10 mg tablets

Statistical Methods

The primary variable was analyzed using a mixed model for repeated measures (MMRM), the response variable was the erectile function score IIEF-15 and change from baseline. Treatment (sacubitril/valsartan versus enalapril), visit and treatment-by-visit interaction were included as fixed-effect factors; baseline IIEF-15 was included as a covariate; the within-patient covariance was modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). The statistical test was performed at the two-sided significance level of 0.05 based on the MMRM model.

The secondary variables were summarized using descriptive statistics. For question no. 5 of the sexual activity dairy, only frequency distribution for each category (yes and no) were provided at week 4 and 12.

The assessment of safety was based on the frequency of AEs, which were summarized by the number and percentage of patients in each primary system organ class and preferred term (PT). Summaries or listings were provided for study medication related AEs, deaths, SAEs, other significant AEs leading to study discontinuation and AEs leading to dose adjustment, as appropriate.

Notably abnormal hematology and blood chemistry values by laboratory parameter, and hematology and blood chemistry laboratory values by treatment were listed. Vital signs were summarized including changes from baseline and listed by treatment group.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Patients with a diagnosis of chronic heart failure (NYHA class II) and reduced ejection fraction (LVEF < 40%)

- Patients must be living in a stable and sexually active heterosexual partnership for at least 6 months prior study start

- Patients must have a mild to moderate erectile dysfunction (determined by using the IIEF-5 questionnaire)

- Patients must be on an ACEI or an ARB at a stable dose for at least 4 weeks prior study start

-Patients must be literate in German

Key Exclusion Criteria:

- History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes, ACEIs, ARBs or NEP inhibitors, as well as known or suspected contraindications to the study drugs

- Previous history of intolerance to recommended target doses of ACEIs or ARBs

- Known history of angioedema

- Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy)

- Symptomatic hypotension

- Impaired renal function

- Penile anatomical defects and Peyronie’s disease

- Diabetes mellitus Type I or insulin-dependent Type II

- Known prostate cancer

Participant Flow Table

Overall Study

	LCZ696	Enalapril	Total
Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg) bid	Enalapril 10 mg bid	
Started	13	14	27
Completed	12	13	25
Not Completed	1	1	2
Adverse Event	1	0	1
Withdrawal by Subject	0	1	1

Baseline Characteristics

	LCZ696	Enalapril	Total
Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg) bid	Enalapril 10 mg bid	
Number of Participants [units: participants]	13	14	27

Sex: Female, Male[1] (units: Participants) Count of Participants (Not Applicable)			
Female	0	0	0
Male	13	14	27
Race (NIH/OMB)[2] (units: Participants) Count of Participants (Not Applicable)			
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
Age Continuous (units: Years) Mean ± Standard Deviation			
	63.5±9.18	66.5±7.80	65.0±8.47

[1] Gender
[2] Race

Primary Outcome Result(s)

Erectile function score using Index of Erectile Function (IIEF-15)

(Time Frame: Week 12 (3 months))

	LCZ696	Enalapril
Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg) bid	Enalapril 10 mg bid
Number of Participants Analyzed [units: participants]	12	13
Erectile function score using Index of Erectile Function (IIEF-15) (units: Scores on a scale) Least Squares Mean ± Standard Error		
	15.1 ± 2.15	12.2 ± 2.00

Statistical Analysis

Groups	LCZ696, Enalapril
P Value	0.3432
Method	Other Mixed Model Repeated Measures (MMRM)
Other LS mean of treatment difference	2.9
Standard Error of the mean	2.94

95 % Confidence Interval 2-Sided	-3.29 to 9.01

Secondary Outcome Result(s)

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

(Time Frame: Baseline, Week 4, Week 12)

	LCZ696	Enalapril
Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg bid)	Enalapril 10 mg bid
Number of Participants Analyzed [units: participants]	13	14
Summary of change from baseline in Self-reported frequency of sexual activity per week (units: Number) Mean ± Standard Deviation		
Week 4:	-1.6 ± 1.59	-1.1 ± 1.97
Week 12:	-1.4 ± 3.13	-2.0 ± 3.07

Summary of change from baseline in NT-proBNP levels

(Time Frame: Baseline, Week 4, Week 12)

	LCZ696	Enalapril
Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg bid)	Enalapril 10 mg bid
Number of Participants Analyzed [units: participants]	13	14

Summary of change from baseline in NT-proBNP levels (units: pg/mL) Median (Inter-Quartile Range)		
Week 4	-369.00 (-521.00 to -68.00)	-43.50 (-123.50 to 363.00)
Week 12	-208.50 (-1469.00 to 416.50)	-189.00 (-394.00 to 10.00)

Safety Results

All-Cause Mortality

	LCZ696 N = 13	Enalapril N = 14
Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg) bid	Enalapril 10 mg bid
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 2 years, 1 month
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (24.0)

Assessment Type for Table Default	Systematic Assessment

	LCZ696 N = 13	Enalapril N = 14
Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg) bid	Enalapril 10 mg bid
Total participants affected	1 (7.69%)	1 (7.14%)
Cardiac disorders		
Cardiac arrest	0 (0.00%)	1 (7.14%)
Vascular disorders		
Hypertensive crisis	1 (7.69%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 2 years, 1 month
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LCZ696 N = 13	Enalapril N = 14

Arm/Group Description	LCZ696 200 mg (sacubitril/valsartan 97 mg/103 mg) bid	Enalapril 10 mg bid
Total participants affected	7 (53.85%)	5 (35.71%)
Gastrointestinal disorders		
Dental caries	1 (7.69%)	0 (0.00%)
Toothache	1 (7.69%)	0 (0.00%)
General disorders and administration site conditions		
Oedema peripheral	0 (0.00%)	1 (7.14%)
Infections and infestations		
Bronchitis	1 (7.69%)	0 (0.00%)
Investigations		
Blood potassium decreased	1 (7.69%)	0 (0.00%)
Metabolism and nutrition disorders		
Fluid retention	0 (0.00%)	1 (7.14%)
Gout	0 (0.00%)	1 (7.14%)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (7.69%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		

Dyspnoea	0 (0.00%)	1 (7.14%)
Vascular disorders		
Haematoma	1 (7.69%)	0 (0.00%)
Hypotension	1 (7.69%)	1 (7.14%)

Conclusion:

Due to low sample size, erectile dysfunction was not significantly improved at Week 12 in the LCZ696 group compared to enalapril group. But, a numerically higher improvement in erectile function score was observed at Week 12 in the LCZ696 group than the enalapril group. The safety profile of LCZ696 in this study was consistent with that observed in other pivotal HFrEF and HFpEF studies. No new safety concerns were identified.

Date of Clinical Trial Report

15-December-2021