Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Sacubitril/valsartan

Trial Indication(s)

Heart failure

Protocol Number

CLCZ696B2228

Protocol Title

A multicenter, randomized, double-blind, parallel group study to assess the safety and tolerability of initiating LCZ696 in heart failure patients comparing two titration regimens

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

15-Nov-2013 to 05-Aug-2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Multi-center, randomized, double-blind, parallel-group study designed to assess the safety and tolerability of initiating LCZ696 in heart failure patients (New York Heart Association class II-IV) with reduced ejection fraction defined by a left ventricular ejection fraction ≤ 35%. The study consisted of two main phases: (1) open-label LCZ696 run-in phase lasting approximately one week, and (2) double-blind randomized phase lasting approximately 11 weeks. Patients enrolled in this study were stratified based on the pre-study level of renin angiotensin aldosterone system inhibition (high/low). Both outpatients and hospitalized patients (inpatients) were eligible for participation in this study. Patients who successfully completed the run-in phase on LCZ696 50 mg bid were randomized to either a condensed up-titration regimen (reaching target dose LCZ696 200 mg bid over 3 weeks) or a conservative up-titration regimen (reaching target dose LCZ696 200 mg bid over 6 weeks) in a 1:1 ratio within each renin angiotensin aldosterone system stratum. Throughout the randomized phase, patients took the study medication in addition to their background heart failure therapy, except for angiotensin converting enzyme inhibitors and angiotensin receptor blockers, which were replaced by the study medication itself.

Centers

137 centers in 11 countries: United States(34), Italy(10), Hungary(9), Spain(8), Bulgaria(6), Turkey(5), Norway(2), Germany(40), Slovakia (Slovak Republic)(9), Finland(4), United Kingdom(10)

Publication

None

Objectives:

Primary Objective:

- To characterize the safety and tolerability of initiating LCZ696 in heart failure with reduced ejection fraction patients with 3-week and 6-week up-titration regimens over 12 weeks based on reported adverse events and laboratory assessments.

Secondary Objectives:

- To evaluate the proportion of patients in the two treatment groups who achieved treatment success, defined as those achieving and maintaining LCZ696 200 mg bid without any dose interruption or down-titration over 12 weeks.
- To evaluate the proportion of patients who tolerate a regimen of LCZ696 200 mg bid for at least 2 weeks leading to study completion, regardless of previous dose interruption or down-titration

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

Oral tablets of valsartan 50 mg, 100 mg and 200 mg with a target dose of LCZ696 200 mg bid during the study.

Statistical Methods

Analyses of primary and secondary variables were performed based on all randomized patients excluding any misrandomized patients. The primary analysis was focused on summarizing incidence rates for each of the four pre-specified adverse events and four pre-specified laboratory assessment outcomes and was performed within each of pre-study high/ low ARB/ACEI dose stratum. The secondary analyses were aimed at estimating rate of treatment success and tolerability. Statistical testing was performed at the two-sided significance level of 0.05 and estimated risk ratios and corresponding 95% confidence intervals were provided, as appropriate for both primary and secondary outcomes. Similar analyses based on the overall patient population (pooled from the two strata) were also performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male and female patients (≥18 years old) diagnosed with heart failure New York Heart Association class II-IV and reduced ejection fraction (left ventricular ejection fraction ≤ 35%), on beta blockers.
- Meeting one of the following criteria: angiotensin converting enzyme inhibitors or angiotensin receptor blockers naïve patients, i.e., not on an angiotensin converting enzyme inhibitors or angiotensin receptor blockers for at least 4 weeks before screening; outpatients who were being treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, dose had to be stable dose for at least 2 weeks before screening; hospitalized patients (inpatients), being on no angiotensin converting enzyme inhibitors/ angiotensin receptor blockers or on a tolerated dose of an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker at screening.

Exclusion criteria:

- Symptomatic hypotension and/or a systolic blood pressure < 100 mmHg or > 180 mmHg; estimated glomerular filtration rate < 30 mL/min/1.73m^2; Serum potassium > 5.2 mmol/L; long QT syndrome or QTc > 450 msec (using the Bazett correction method) for males and > 470 msec for females
- History of intolerance to recommended target doses of angiotensin converting enzyme inhibitors or angiotensin receptor blockers; hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, angiotensin receptor blockers, or neutral endopeptidase inhibitors; electrocardiogram abnormalities that indicated significant risk of safety for patients or QT syndrome or angioedema; severe pulmonary disease; cardiomyopathy

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Patient disposition (Randomized set)

Disposition Reason	LCZ696 Condensed N=247 n (%)	LCZ696 Conservative N=251 n (%)	Total N=498 n (%)
Completed	208 (84.2)	221 (88.0)	429 (86.1)
Discontinued from the study	39 (15.8)	30 (12.0)	69 (13.9)
Primary reason for discontinuation in post-randomization period			
Adverse Event(s)	18 (7.3)	13 (5.2)	31 (6.2)
Protocol deviation	10 (4.0)	7 (2.8)	17 (3.4)
Subject withdrew consent	3 (1.2)	4 (1.6)	7 (1.4)
Administrative problems	4 (1.6)	1 (0.4)	5 (1.0)
Physician's decision	2 (0.8)	3 (1.2)	5 (1.0)
Death	2 (0.8)	1 (0.4)	3 (0.6)
Lost to follow-up	0 (0.0)	1 (0.4)	1 (0.2)

Percentages (%) are calculated using the Randomized set as the denominator.

Baseline Characteristics

Demographic and baseline characteristics (Full Analysis Set)

Variable/ Statistic/category	LCZ696 Condensed N=247	LCZ696 Conservative N=251	Total N=498
Age (years)			
N	247	251	498
Mean (SD)	64.2 (11.86)	63.8 (10.94)	64.0 (11.39)
Age category - n (%)			
< 65 years	117 (47.4%)	133 (53.0%)	250 (50.2%)
≥ 65 years	130 (52.6%)	118 (47.0%)	248 (49.8%)
< 75 years	191 (77.3%)	209 (83.3%)	400 (80.3%)
≥ 75 years	56 (22.7%)	42 (16.7%)	98 (19.7%)
Gender - n (%)			
Male	191 (77.3%)	201 (80.1%)	392 (78.7%)
Female	56 (22.7%)	50 (19.9%)	106 (21.3%)
Predominant race - n (%)			
Caucasian	228 (92.3%)	234(93.2%)	462(92.8%)
Black	12 (4.9%)	11 (4.4%)	23 (4.6%)
Asian	0 (0.0%)	1 (0.4%)	1 (0.2%)
Other	7 (2.8%)	5 (2.0%)	12 (2.4%)
Ethnicity			
Hispanic/Latino	27(10.9%)	28(11.2%)	55(11.0%)
Indian (Indian subcontinent)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Mixed Ethnicity	4 (1.6%)	6 (2.4%)	10 (2.0%)
Other	215 (87.0%)	217 (86.5%)	432 (86.7%)
Region (1)			
North America	34 (13.8%)	33 (13.1%)	67 (13.5%)
Western Europe	117 (47.4%)	118 (47.0%)	235 (47.2%)
Central Europe	96 (38.9%)	100 (39.8%)	196 (39.4%)
Patients composition			
Inpatient	25 (10.1%)	31 (12.4%)	56 (11.2%)
Outpatient	222 (89.9%)	220 (87.6%)	442 (88.8%)
High RAAS	120 (48.6%)	127 (50.6%)	247 (49.6%)

Variable/ Statistic/category	LCZ696 Condensed N=247	LCZ696 Conservative N=251	Total N=498
Low RAAS	127 (51.4%)	124 (49.4%)	251 (50.4%)
Low RAAS – Treated with ARB or ACEI	110 (44.5%)	108 (43.0%)	218 (43.8%)
Low RAAS- naïve (2)	17 (6.9%)	16 (6.4%)	33 (6.6%)
Baseline LVEF at Visit 1 (%)			
N	247	250	497
Mean (SD)	29.8 (5.15)	29.6 (5.36)	29.7 (5.25)
Missing	0	1	1
Baseline LVEF group – n (%)			
< 30%	84 (34.0%)	83 (33.1%)	167 (33.5%)
≥ 30% to ≤ 35%	163 (66.0%)	167 (66.5%)	330 (66.3%)
Missing	0 (0.0%)	1 (0.4%)	1 (0.2%)
NYHA class at Visit 1 - n (%)			
II	175 (70.9%)	178 (70.9%)	353 (70.9%)
III	72 (29.1%)	72 (28.7%)	144 (28.9%)
IV	0 (0.0%)	1 (0.4%)	1 (0.2%)
Weight (kg) at Visit 1			
N	247	250	497
Mean (SD)	90.1 (19.91)	90.0 (20.80)	90.1 (20.34)
Body Mass Index (kg/m2) at Visit 1**			
N	246	248	494
Mean (SD)	30.9 (5.88)	30.6 (6.03)	30.8 (5.95)
SBP (mmHg) at Visit 2			
N	247	251	498
Mean (SD)	130.8 (16.64)	130.8 (15.98)	130.8 (16.30)
DBP (mmHg) at Visit 2			
N	247	251	498
Mean (SD)	77.2 (9.99)	77.6 (9.26)	77.4 (9.62)
Baseline eGFR (mL/min/1.73 m^2) at Visit 1			
N	246	249	495
Mean (SD)	69.6 (21.63)	70.6 (25.16)	70.1 (23.45)
Baseline eGFR group (mL/min/1.73 m^2) at Visit 1 - n (%)			

Variable/ Statistic/category	LCZ696 Condensed N=247	LCZ696 Conservative N=251	Total N=498
< 60 (mL/min/1.73 m^2)	83 (33.6%)	85 (33.9%)	168 (33.7%)
≥ 60 (mL/min/1.73 m^2)	163 (66.0%)	164 (65.3%)	327 (65.7%)
Missing	1 (0.4%)	2 (0.8%)	3 (0.6%)

BMI (body mass index) is calculated as: [weight (kg)/ [height (m^2)]
(1) Region Description:
North America: USA
Western Europe: Finland, Germany, Italy, Spain, Turkey, UK.
Central Europe: Bulgaria, Hungary, Slovakia
(2) Patients not on ARB or ACEI for 4 weeks prior to screening are summarized under Low RAAS- naïve group.

Summary of Efficacy

Primary Outcome Result(s)

Analysis of primary variables: number (%) of patients experiencing hypotension, renal dysfunction, hyperkalemia and angioedema during post-randomization period (Full Analysis Set)

Response variable	Stratum	LCZ696 Condensed n/N (%)	LCZ696 Conservative n/N (%)
Hypotension	High RAAS	5/120 (4.2)	7/127 (5.5)
	Low RAAS	19/127 (15.0)	14/124 (11.3)
	All	24/247 (9.7)	21/251 (8.4)
Renal dysfunction	High RAAS	5/120 (4.2)	9/127 (7.1)
	Low RAAS	13/127 (10.2)	10/124 (8.1)
	All	18/247 (7.3)	19/251 (7.6)
Hyperkalemia	High RAAS	8/120 (6.7)	5/127 (3.9)
	Low RAAS	11/127 (8.7)	6/124 (4.8)
	All	19/247 (7.7)	11/251 (4.4)
Angioedema	High RAAS	0/120 (0.0)	1/127 (0.8)
	Low RAAS	0/127 (0.0)	1/124 (0.8)
	All	0/247 (0.0)	2/251 (0.8)

n: Total number of patients with specified adverse events included in the analysis.
N: Total number of patients included in the analysis.

Analysis of primary variables: number (%) of patients experiencing abnormal central laboratory and vital signs outcomes during post-randomization period (Full Analysis Set)

Response variable	Stratum	LCZ696 Condensed n/N (%)	LCZ696 Conservative n/N (%)
SBP < 95 mmHg	High RAAS	4/120 (3.3)	7/126 (5.6)
	Low RAAS	18/126 (14.3)	6/123 (4.9)
	All	22/246 (8.9)	13/249 (5.2)
Serum potassium > 5.5 mmol/L	High RAAS	9/119 (7.6)	6/125 (4.8)
	Low RAAS	9/126 (7.1)	4/122 (3.3)
	All	18/245 (7.3)	10/247 (4.0)
Serum potassium ≥ 6.0 mmol/L	High RAAS	2/119 (1.7)	0/125 (0.0)
	Low RAAS	1/126 (0.8)	1/122 (0.8)
	All	3/245 (1.2)	1/247 (0.4)
Serum creatinine > 3.0 mg/dL (267 µmol/L).	High RAAS	0/119 (0.0)	0/125 (0.0)
	Low RAAS	1/126 (0.8)	0/123 (0.0)
	All	1/245 (0.4)	0/248 (0.0)
Doubling of serum creatinine 200% of the baseline	High RAAS	0/119 (0.0)	0/125 (0.0)
	Low RAAS	2/126 (1.6)	1/123 (0.8)
	All	2/245 (0.8)	1/248 (0.4)

n: Total number of patients with specified adverse events included in the analysis.
N: Total number of patients included in the analysis.

Secondary Outcome Result(s)

Overall treatment success and tolerability over 12 weeks of treatment

	High RAAS	Low RAAS	Total
LCZ696 200 mg bid achieved and had no dose adjustment/interruption through 12 weeks			
Run-in + Randomized: excluding non AE-related discontinuations (N=496)	188/247 (76.1%)	190/249 (76.3%)	378/496 (76.2%)
Run-in + Randomized (N=538)	188/274 (68.6%)	190/264 (72.0%)	378/538 (70.3%)
LCZ696 200 mg bid achieved and maintained for at least 2 weeks prior to study completion			
Run-in + Randomized: excluding non AE-related discontinuations (N=496)	197/247 (79.8%)	200/249 (80.3%)	397/496 (80.0%)
Run-in + Randomized (N=538)	197/274 (71.9%)	200/264 (75.8%)	397/538 (73.8%)

Analysis of secondary variables: between-treatment analysis for treatment success and tolerability of LCZ696 200 mg bid for at least two weeks leading to study completion (Full Analysis Set)

Secondary variables	Stratum	Total n/N (%)	LCZ696 Condensed n/N (%)	LCZ696 Conservative n/N (%)	Odds ratio (95% CI)	p-value
Treatment success	High RAAS	188/226 (83.2)	90/109 (82.6)	98/117 (83.8)	0.91 (0.45, 1.83)	0.7827
	Low RAAS	190/240 (79.2)	89/121 (73.6)	101/119 (84.9)	0.50 (0.26, 0.94)	0.0302
	All	378/466 (81.1)	179/230 (77.8)	199/236 (84.3)	0.65 (0.41, 1.05)	0.0781
Tolerability	High RAAS	197/226 (87.2)	94/109 (86.2)	103/117 (88.0)	0.84 (0.38, 1.84)	0.6569
	Low RAAS	200/240 (83.3)	97/121 (80.2)	103/119 (86.6)	0.63 (0.32, 1.26)	0.1894
	All	397/466 (85.2)	191/230 (83.0)	206/236 (87.3)	0.72 (0.43, 1.20)	0.2072

n: total number of successes included in the analysis
N: total number of patients included in the analysis (excluding patients discontinued for reasons other than AE or death)
Odds ratio, 95% CI and p-values for each stratum from the logistic regression model with treatment group and region as fixed factors fitted within each stratum, whereas overall estimates are from the logistic regression with treatment, region and stratum as fixed factors. The p-value is from the Likelihood Ratio test.
Patient B2228-702-00026 was considered to have achieved treatment success despite the fact that the investigator had mistakenly interrupted the blinded study medication without the patient having experienced an AE, however the patient continued on open-label LCZ696 200 mg bid.

Summary of Safety

Safety Results Adverse events by primary system organ class (Safety set)

Primary system organ class	LCZ696 Condensed N=246 n (%)	LCZ696 Conservative N=251 n (%)	Total N=497 n (%)
-Any adverse event	127 (51.6)	106(42.2)	233 (46.9)
Blood and lymphatic system disorders	2(0.8)	2(0.8)	4 (0.8)
Cardiac disorders	30 (12.2)	18 (7.2)	48 (9.7)
Ear and labyrinth disorders	9 (3.7)	3 (1.2)	12 (2.4)
Eye disorders	2 (0.8)	0 (0.0)	2 (0.4)
Gastrointestinal disorders	10 (4.1)	14 (5.6)	24 (4.8)
General disorders and administration site conditions	8 (3.3)	14 (5.6)	22 (4.4)
Hepatobiliary disorders	1 (0.4)	2 (0.8)	3 (0.6)
Infections and infestations	22 (8.9)	10 (4.0)	32 (6.4)
Injury, poisoning and procedural complications	5 (2.0)	4 (1.6)	9 (1.8)
Investigations	18 (7.3)	13 (5.2)	31 (6.2)
Metabolism and nutrition disorders	26 (10.6)	20 (8.0)	46 (9.3)
Musculoskeletal and connective tissue disorders	12 (4.9)	10 (4.0)	22 (4.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.8)	0 (0.0)	2 (0.4)
Nervous system disorders	20 (8.1)	15 (6.0)	35 (7.0)
Psychiatric disorders	1 (0.4)	2 (0.8)	3 (0.6)
Renal and urinary disorders	16 (6.5)	15 (6.0)	31 (6.2)
Reproductive system and breast disorders	3 (1.2)	3 (1.2)	6 (1.2)
Respiratory, thoracic and mediastinal disorders	4 (1.6)	14 (5.6)	18 (3.6)
Skin and subcutaneous tissue disorders	9 (3.7)	9 (3.6)	18 (3.6)
Vascular disorders	30 (12.2)	26 (10.4)	56 (11.3)

Primary system organ class	LCZ696 Condensed N=246 n (%)	LCZ696 Conservative N=251 n (%)	Total N=497 n (%)

Primary system organ classes (SOC) are presented alphabetically.
Patients with multiple events within a primary SOC are counted only once in the relevant category.

Most common adverse events (at least 2% in any treatment group) (Safety set)

Preferred term	LCZ696 Condensed N=246 n (%)	LCZ696 Conservative N=251 n (%)	Total N=497 n (%)
-Any adverse event	127 (51.6)	106 (42.2)	233 (46.9)
Hypotension	24 (9.8)	21 (8.4)	45 (9.1)
Hyperkalemia	16 (6.5)	11 (4.4)	27 (5.4)
Dizziness	9 (3.7)	6 (2.4)	15 (3.0)
Renal impairment	10 (4.1)	4 (1.6)	14 (2.8)
Cardiac failure	9 (3.7)	3 (1.2)	12 (2.4)
Renal failure	2 (0.8)	8 (3.2)	10 (2.0)
Vertigo	7 (2.8)	3 (1.2)	10 (2.0)
Nasopharyngitis	6 (2.4)	3 (1.2)	9 (1.8)
Cough	2 (0.8)	6 (2.4)	8 (1.6)
Hypokalemia	6 (2.4)	2 (0.8)	8 (1.6)
Back pain	5 (2.0)	2 (0.8)	7 (1.4)
Glomerular filtration rate decreased	2 (0.8)	5 (2.0)	7 (1.4)

Preferred terms are sorted by descending frequency in the Total column.
Patients with multiple events within a preferred term (PT) are counted only once in the relevant category.

Deaths, other serious or clinically significant adverse events or related discontinuations from study during post-randomization period (Safety set)

	LCZ696 Condensed N=246 n (%)	LCZ696 Conservative N=251 n (%)	Total N=497 n (%)
Deaths	2 (0.8)	1 (0.4)	3 (0.6)
SAEs	21 (8.5)	14 (5.6)	35 (7.0)
Discontinuations due to AEs	20 (8.1)	14 (5.6)	34 (6.8)

Other Relevant Findings

None

Conclusion:

The majority of patients in this study were able to achieve the LCZ696 200 mg bid target dose, regardless of baseline renin angiotensin aldosterone system exposure. During the randomized period and excluding patients who discontinued due to non-adverse event related reasons, 81% of patients achieved the target dose of LCZ696 200 mg bid and did not have any dose adjustment or interruption through the entire 12-week study period, and 85% were on target dose for at least 2 weeks leading to study completion. Across both run-in and randomized periods, the LCZ696 200 mg bid target dose was achieved with no dose adjustment or interruption over 12 weeks by 76% of patients excluding discontinuations due to non-adverse event related reasons and by 70% of all treated patients. While there was no difference in tolerability due to the up-titration regimen in patients on higher pre-study doses of angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, more patients on lower pre-study doses of angiotensin converting enzyme inhibitors/ angiotensin receptor blockers were able to achieve the target 200 mg bid dose if up-titrated more gradually.

Date of Clinical Trial Report

07-Nov-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

21-Jul-2015

Date of Latest Update

Reason for Update