Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

LCZ696 (sacubitril/valsartan)

Trial Indication(s)

Chronic heart failure (CHF) with reduced ejection fraction (EF)

Protocol Number

CLCZ696B2314

Protocol Title

A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

08 Dec 2009 (first patient first visit) to 21 May 2014 (last patient last visit)

Reason for Termination (If applicable)

The Data Monitoring Committee (DMC) for CLCZ696B2314 (PARADIGM-HF) conducted the final pre-specified interim analysis on 28-Mar-2014 and unanimously recommended early termination of the trial due to compelling efficacy of LCZ696 in patients with HF and reduced EF. The PARADIGM-HF Executive Committee accepted the DMC's recommendation on 28-Mar-2014 after consultation with Novartis.

Study Design/Methodology

This study was designed to evaluate the efficacy and safety of LCZ696 200 mg bid as compared to enalapril 10 mg bid, on mortality and morbidity (Primary endpoint: composite of cardiovascular [CV] death or first hospitalization for heart failure [HF]) reduction in patients with HF and reduced ejection fraction. The study was powered for CV mortality alone. The trial consisted of two periods: (1) a single-blind active run-in period that lasted between 5 to 10 weeks, in which patients received enalapril 10 mg bid, followed by LCZ696 100 mg bid and then LCZ696 200 mg bid and (2) a double-blind randomized treatment period (LCZ696 200 mg bid or enalapril 10 mg bid), that lasted up to 51 months.

Centers

984 sites randomized at least one patient in 47 countries worldwide: USA (124 sites), Canada (24), Argentina (46), Brazil (30), Chile (8), Colombia (14), Dominican Republic (3), Ecuador (5), Guatemala (11), Mexico (14), Panama (4), Peru (10), Venezuela (5), Belgium (13), Denmark (9), Finland (5), France (25), Germany (79), Iceland (4), Italy (32), Netherlands (20), Portugal (10), Spain (21), Sweden (9), Israel (9), South Africa (34), United Kingdom (47), Bulgaria (29), Czech Republic (25), Estonia (4), Hungary (31), Latvia (5), Lithuania (5), Poland (18), Rep. of Slovakia (24), Romania (18), Russia (90), Turkey (12), China (16), Hong Kong (4), India (44), Republic of Korea (11), Malaysia (3), Philippines (14), Singapore (4), Taiwan (8), Thailand (4).

Publication

McMurray JJV, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail. 2013;15:1062-73
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3746839/

McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
http://www.nejm.org/doi/full/10.1056/NEJMoa1409077

Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation. 2015;131(1):54-61.
http://circ.ahajournals.org/content/131/1/54.long

Objectives:

Primary objective

The primary objective of this study was to test if LCZ696 is superior to enalapril in delaying time to first occurrence of the composite endpoint, which was defined as either CV death or HF hospitalization, in patients with HF (NYHA class II – IV) and reduced left ventricular EF (≤ 40%, changed to ≤ 35% by Protocol Amendment 1).

Secondary objectives

The secondary objectives were:

- To test whether LCZ696 is superior to enalapril in delaying the time to all-cause mortality;
- To test whether LCZ696, compared to enalapril, improves the clinical summary score for HF symptoms and physical limitations, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), at 8 months;
- To test whether LCZ696 is superior to enalapril in delaying time to new onset atrial fibrillation and
- To test whether LCZ696 is superior to enalapril in delaying the time to first occurrence of either (1) a 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline, (2) >30 mL/min/1.73 m^2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73 m^2, or (3) reaching end stage renal disease (ESRD).

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

Test product, dose and mode of administration: The target dose during the study was LCZ696 200 mg bid given orally. LCZ696 was supplied as 50 mg, 100 mg and 200 mg film-coated tablets.

Reference therapy, dose and mode of administration: The target dose during the study was enalapril 10 mg bid given orally. Enalapril was provided as 2.5 mg, 5 mg and 10 mg film-coated tablets.

Statistical Methods

The primary efficacy variable was analyzed using the Cox proportional hazards model with treatment and region as fixed-effect factors. The estimated hazard ratio (HR) and the corresponding two-sided 95% confidence interval and one-sided p-values were provided. The full analysis set (FAS) was used for the primary analysis. Similarly, the above analysis was repeated for the per protocol (PP) population as a supportive analysis.

The overall type I error was planned to be controlled at 2.5% (one-sided) with adjustment for the interim efficacy analyses (IAs). Since the study was stopped at the 3rd IA, the significance level allocated to this IA (one-sided α=0.001) was used for the formal significance test of the primary endpoint in the final analysis.

Pre-specified subgroup analyses were performed for the FAS. To explore the consistency of beneficial effects in subgroups, the estimated hazard ratio (HR), two-sided 95% confidence interval, and p-value were provided for each of the subgroups based on the Cox proportional hazards model in which treatment and region were included as fixed-effect factors. Interaction between the subgroup and treatment was evaluated and p-values were provided using the above model plus additional terms for subgroup and the interaction between subgroup and treatment. No adjustment for multiple comparisons was made for subgroup analyses.

The secondary hypotheses were formally tested and statistical inferences were made only if the primary hypothesis was rejected. The four secondary efficacy variables were tested for superiority of LCZ696 to enalapril for the FAS. For each secondary variable, the null hypothesis of no treatment difference between LCZ696 and enalapril was tested against the alternative hypothesis that LCZ696 was more effective than enalapril. A sequentially rejective multiple test procedure (MTP) was used for the secondary efficacy comparisons in order to provide strong family-wise control of the α level, across the primary and all secondary endpoints, across all potential interim and final analyses.

The assessment of safety was based primarily on the frequency of adverse events (AEs), serious AEs (SAEs), and laboratory abnormalities that occurred in the run-in periods and double-blind period. Data from other tests (e.g., electrocardiogram (ECG) or vital signs) were listed, notable values were flagged, and any other information collected was listed as appropriate. Safety analyses were performed based on the safety population (SAF). The safety topics of special interest included: hypotension, renal impairment, hyperkalemia, angioedema, developmental toxicity, hypersensitivity reaction, hepatotoxicity, change in bone growth/bone mineral density, cognitive impairment, stimulation of lipolysis, gastric lesions, QT prolongation and cancer promotion.

It was planned to have three interim efficacy analyses at approximately 1/3, 1/2 and 2/3 of information time. The Haybittle-Peto type of boundary was used for the IA to assess superiority, with the boundary spent approximately an alpha of 0.0001 (one-sided) at the first IA and 0.001 (one-sided and nominal) at the second and third interim analyses. For each IA, the analysis dataset comprised all patients who were randomized before the IA cutoff date. Interim analyses were performed by an independent statistician who was not involved in the trial conduct. The results were reviewed by the independent DMC. Investigators, Novartis employees, and others who were involved in the conduct of the trial remained blinded to the treatment codes until the database had been locked for final analysis.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients must give written informed consent before any assessment is performed.
- Outpatients ≥ 18 years of age, male or female.
- Patients with a diagnosis of CHF NYHA class II-IV with LVEF ≤ 40%, changed to ≤ 35% by Protocol Amendment 1.
- B-type natriuretic peptide (BNP) ≥ 150 pg/ml (or N-terminal prohormone B-type natriuretic peptide [NT-proBNP] ≥ 600 pg/ml) or BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/ml) and a hospitalization for HF within the last 12 months.
- Patients must be on an ACEI or an ARB at a stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks.
- Patients must be treated with a β-blocker, unless contraindicated or not tolerated, at a stable dose for at least 4 weeks.
- Other evidence-based therapy for HF, including an aldosterone antagonist, should be considered, as recommended by guidelines.

Exclusion Criteria:

- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
- History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, angiotensin receptor blockers (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.
- Requirement of treatment with both ACEIs and ARBs.
- Current acute decompensated HF (exacerbation of CHF manifested by signs and symptoms that may require intravenous therapy).
- Symptomatic hypotension and/or a systolic blood pressure (SBP) < 100 mmHg at Visit 1 (screening) or < 95 mmHg at Visit 3 or Visit 5 (randomization).
- eGFR < 30 mL/min/1.73m^2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula
- Serum potassium > 5.2 mmol/L at Visit 1 (screening) or > 5.4 mmol/L at Visit 3 or Visit 5 (randomization).
- Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Patient disposition and vital status by treatment group (Screened set)

Disposition and vital status at study end	LCZ696 n (%)	Enalapril n (%)	Total n (%)
Screen set			18071 (100)
Screen failure			7534 (41.69)
Run-in set (2)			10521 (100)
Enalapril run-in (3)			10513 (99.92)
Failed in enalapril run-in			1102 (10.47)
Dead			55 (0.52)
LCZ696 run-in			9419 (89.53)
Failed in LCZ696 run-in			982 (9.33)
Dead			63 (0.60)
Run-in failure			2084 (19.81)
Randomized			6 (0.06)
Run-in complete			8437 (80.19)
Not randomized			1 (0.01)
Randomized set	4209 (100)	4233 (100)	8442 (100)
Mis-randomized	4 (0.10)	2 (0.05)	6 (0.07)
GCP violations	18 (0.43)	19 (0.45)	37 (0.44)
Discontinued from double-blind period	8 (0.19)	10 (0.24)	18 (0.21)
Dead	2 (0.05)	2 (0.05)	4 (0.05)
Lost to follow-up	5 (0.12)	7 (0.17)	12 (0.14)
Patient’s request	1 (0.02)	1 (0.02)	2 (0.02)
Full analysis set	4187 (99.48)	4212 (99.50)	8399 (99.49)
Discontinued from double-blind period	741 (17.61)	862 (20.36)	1603 (18.99)
Dead	724 (17.20)	844 (19.94)	1568 (18.57)
Lost to follow-up	2 (0.05)	5 (0.12)	7 (0.08)
Patient’s request	15 (0.36)	13 (0.31)	28 (0.33)
Known to be alive at close-out	4 (0.10)	6 (0.14)	10 (0.12)

Disposition and vital status at study end	LCZ696 n (%)	Enalapril n (%)	Total n (%)
Known to be dead at close-out	2 (0.05)	3 (0.07)	5 (0.06)
Vital status unknown at close-out	9 (0.21)	4 (0.09)	13 (0.15)
Safety set	4203 (99.86)	4229 (99.91)	8432 (99.88)
Per-protocol set	4166 (98.98)	4187 (98.91)	8353 (98.95)

Reasons for treatment discontinuation during double-blind period (Randomized set)

	LCZ696 N=4209 n (%)	Enalapril N=4233 n (%)	Total N=8442 n (%)
Patients who never received study treatment during double-blind period	6 (0.14)	4 (0.09)	10 (0.12)
Patients who permanently discontinued study treatment during double-blind period	1182 (28.08)	1353 (31.96)	2535 (30.03)
Primary reason for EOS treatment			
AE(s)	437 (10.38)	510 (12.05)	947 (11.22)
Abnormal laboratory value(s)	7 (0.17)	6 (0.14)	13 (0.15)
Unsatisfactory therapeutic effect	0 (0.00)	1 (0.02)	1 (0.01)
Patient's condition no longer requires study drug	3 (0.07)	4 (0.09)	7 (0.08)
Lost to follow-up	8 (0.19)	8 (0.19)	16 (0.19)
Administrative problems	12 (0.29)	9 (0.21)	21 (0.25)
Death	430 (10.22)	512 (12.10)	942 (11.16)
Protocol deviation	5 (0.12)	3 (0.07)	8 (0.09)
Patient's request	208 (4.94)	219 (5.17)	427 (5.06)
Other	72 (1.71)	81 (1.91)	153 (1.81)
Missing end of treatment	5 (0.12)	3 (0.07)	8 (0.09)
Patients completed study treatment	3022 (71.80)	2877 (67.97)	5899 (69.88)

Patient demographic and disease characteristics for double-blind period by treatment group (Randomized set)

Variable/ Statistic/category	LCZ696 N=4209	Enalapril N=4233	Total N=8442
Age (years)			
n	4209	4233	8442
Mean	63.78	63.82	63.80
SD	11.520	11.250	11.385
Age category - n (%)			
< 65 years	2122 (50.42)	2177 (51.43)	4299 (50.92)
>= 65 years	2087 (49.58)	2056 (48.57)	4143 (49.08)
< 75 years	3423 (81.33)	3450 (81.50)	6873 (81.41)
>= 75 years	786 (18.67)	783 (18.50)	1569 (18.59)
Gender - n (%)			
Male	3321 (78.90)	3274 (77.34)	6595 (78.12)
Female	888 (21.10)	959 (22.66)	1847 (21.88)
Predominant race - n (%)			
Caucasian	2780 (66.05)	2799 (66.12)	5579 (66.09)
Black	213 (5.06)	215 (5.08)	428 (5.07)
Asian	760 (18.06)	750 (17.72)	1510 (17.89)
Native American	84 (2.00)	88 (2.08)	172 (2.04)
Pacific Islander	0 (0.00)	1 (0.02)	1 (0.01)
Other	372 (8.84)	380 (8.98)	752 (8.91)
Ethnicity - n (%)			
Hispanic/Latino	777 (18.46)	778 (18.38)	1555 (18.42)
Chinese	242 (5.75)	251 (5.93)	493 (5.84)
Indian	335 (7.96)	333 (7.87)	668 (7.91)
Japanese	2 (0.05)	0 (0.00)	2 (0.02)
Mixed ethnicity	32 (0.76)	39 (0.92)	71 (0.84)
Other	2821 (67.02)	2832 (66.90)	5653 (66.96)
Region			
North America	310 (7.37)	292 (6.90)	602 (7.13)
Latin America	726 (17.25)	732 (17.29)	1458 (17.27)
Western Europe	1029 (24.45)	1028 (24.29)	2057 (24.37)
Central Europe	1398 (33.21)	1439 (33.99)	2837 (33.61)

Variable/ Statistic/category	LCZ696 N=4209	Enalapril N=4233	Total N=8442
Asia/Pacific and other	746 (17.72)	742 (17.53)	1488 (17.63)
Baseline LVEF (%)			
n	4209	4232	8441
Mean	29.55	29.41	29.48
SD	6.143	6.287	6.216
Baseline LVEF group- n (%)			
<= 35%	3736 (88.76)	3742 (88.40)	7478 (88.58)
> 35%	473 (11.24)	490 (11.58)	963 (11.41)
NYHA class at Visit 5 (double-blind phase baseline)- n (%)			
Class I	183 (4.35)	213 (5.03)	396 (4.69)
Class II	3007 (71.44)	2930 (69.22)	5937 (70.33)
Class III	979 (23.26)	1056 (24.95)	2035 (24.11)
Class IV	33 (0.78)	27 (0.64)	60 (0.71)
BMI (kg/m^2)			
n	4203	4229	8432
Mean	28.14	28.20	28.17
SD	5.528	5.535	5.531
Baseline SBP (mmHg)			
n	4209	4233	8442
Mean	121.53	121.22	121.38
SD	15.211	15.438	15.325
Baseline eGFR (mL/min/1.73 m^2)			
n	4209	4233	8442
Mean	67.60	67.73	67.66
SD	19.876	20.329	20.103
Baseline eGFR group - n (%)			
< 60 (mL/min/1.73 m^2)	1552 (36.87)	1530 (36.14)	3082 (36.51)
>= 60 (mL/min/1.73 m^2)	2657 (63.13)	2703 (63.86)	5360 (63.49)
Baseline NT-proBNP (pmol/L)			
n	4204	4224	8428
Mean	341.68	341.16	341.42
SD	473.070	466.065	469.544

Variable/ Statistic/category	LCZ696 N=4209	Enalapril N=4233	Total N=8442
Baseline BNP (pmol/L)			
n	4183	4199	8382
Mean	120.69	120.60	120.64
SD	155.030	156.570	155.794
Hypertension at baseline - n (%)			
Yes	2980 (70.80)	2990 (70.64)	5970 (70.72)
No	1229 (29.20)	1243 (29.36)	2472 (29.28)
Diabetic at baseline - n (%)			
Yes	1462 (34.74)	1465 (34.61)	2927 (34.67)
No	2747 (65.26)	2768 (65.39)	5515 (65.33)

Summary of Efficacy

Primary Outcome Result(s)

Primary efficacy analysis of Clinical Endpoint Committee (CEC) confirmed first primary endpoint (CV death, HF hospitalization) and its components for double-blind period (FAS)

					LCZ696 vs Enalapril	
Response variable	LCZ696 n/N (%)	Enalapril n/N (%)	LCZ696 n/T (EAIR) (95% CI)	Enalapril n/T (EAIR) (95% CI)	HR (95% CI)	p-value
Primary Composite	914/4187 (21.83)	1117/4212 (26.52)	914/87.22 (10.48) (9.81,11.18)	1117/84.93 (13.15) (12.39,13.95)	0.80 (0.73,0.87)	<.0001
CV death	558/4187 (13.33)	693/4212 (16.45)	558/93.08 (5.99) (5.51,6.51)	693/92.35 (7.50) (6.96,8.08)	0.80 (0.71,0.89)	<.0001
1st HF Hospitalization	537/4187 (12.83)	658/4212 (15.62)	537/87.22 (6.16) (5.65,6.70)	658/84.93 (7.75) (7.17,8.36)	0.79 (0.71,0.89)	<.0001

Secondary Outcome Result(s)

Between-treatment comparison of all-cause mortality (FAS)

					LCZ696 vs Enalapril	
Response variable	LCZ696 n/N (%)	Enalapril n/N (%)	LCZ696 n/T (EAIR) (95% CI)	Enalapril n/T (EAIR) (95% CI)	HR (95% CI)	p-value
All-cause death	711/4187 (16.98)	835/4212 (19.82)	711/93.08 (7.639) (7.088,8.221)	835/92.35 (9.042) (8.439,9.677)	0.8445 (0.7642,0.9334)	0.0005

Between-treatment analysis for change from baseline to Month 8 for the KCCQ clinical summary score and KCCQ subdomain scores for double-blind period (FAS)

					LCZ696 vs. Enalapril		
	LCZ696 N=3833		Enalapril N=3873			p-value	
	n	LSM of CFB (SE)	n	LSM of CFB (SE)	LSM of difference (95% CI)	2-sided	1-sided
Clinical summary score	3643	-2.99 (0.364)	3638	-4.63 (0.364)	1.64 (0.63, 2.65)	0.0014	0.0007

Between-treatment comparison of first confirmed renal dysfunction event and new onset of atrial fibrillation (FAS)

					LCZ696 vs Enalapril	
Response variable	LCZ696 n/N (%)	Enalapril n/N (%)	LCZ696 n/T (EAIR) (95% CI)	Enalapril n/T (EAIR) (95% CI)	HR (95% CI)	p-value
Renal dysfunction	94/4187 (2.25)	108/4212 (2.56)	94/91.97 (1.022) (0.826,1.251)	108/91.20 (1.184) (0.971,1.430)	0.8600 (0.652,1.134)	0.1424
Time to the first new onset of AF	84/2670 (3.15)	83/2638 (3.15)	84/58.09 (1.446) (1.153,1.790)	83/56.38 (1.472) (1.173,1.825)	0.9686 (0.7151,1.3119)	0.4183

Summary of Safety

Safety Results

Overall summary of AEs during double-blind period (Safety set)

	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Patients with at least one AE	3419 (81.3)	3503 (82.8)	6922 (82.1)
Patients with at least one serious AE	1937 (46.1)	2142 (50.7)	4079 (48.4)
Patients who died	729 (17.3)	848 (20.1)	1577 (18.7)
Patients who discontinued study drug due to AEs	450 (10.7)	516 (12.2)	966 (11.5)
Discontinued study drug due to SAEs	345 (8.2)	399 (9.4)	744 (8.8)
Discontinued study drug due to non-serious AEs	117 (2.8)	134 (3.2)	251 (3.0)

Incidence of AEs during the double-blind period by primary system organ class and treatment group (Safety set)

Primary system organ class	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Number of patients with at least one AE	3419 (81.35)	3503 (82.83)	6922 (82.09)
Blood and lymphatic system disorders	272 (6.47)	288 (6.81)	560 (6.64)
Cardiac disorders	1609 (38.28)	1777 (42.02)	3386 (40.16)
Congenital, familial and genetic disorders	5 (0.12)	17 (0.40)	22 (0.26)
Ear and labyrinth disorders	110 (2.62)	99 (2.34)	209 (2.48)
Endocrine disorders	71 (1.69)	75 (1.77)	146 (1.73)
Eye disorders	178 (4.24)	161 (3.81)	339 (4.02)
Gastrointestinal disorders	809 (19.25)	843 (19.93)	1652 (19.59)
General disorders and administration site conditions	900 (21.41)	984 (23.27)	1884 (22.34)
Hepatobiliary disorders	132 (3.14)	162 (3.83)	294 (3.49)
Immune system disorders	30 (0.71)	38 (0.90)	68 (0.81)
Infections and infestations	1366 (32.50)	1400 (33.10)	2766 (32.80)
Injury, poisoning and procedural complications	386 (9.18)	374 (8.84)	760 (9.01)
Investigations	385 (9.16)	396 (9.36)	781 (9.26)
Metabolism and nutrition disorders	1137 (27.05)	1203 (28.45)	2340 (27.75)
Musculoskeletal and connective tissue disorders	678 (16.13)	672 (15.89)	1350 (16.01)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	183 (4.35)	210 (4.97)	393 (4.66)
Nervous system disorders	770 (18.32)	758 (17.92)	1528 (18.12)
Pregnancy, puerperium and perinatal conditions	4 (0.10)	0 (0.00)	4 (0.05)
Psychiatric disorders	251 (5.97)	256 (6.05)	507 (6.01)
Renal and urinary disorders	757 (18.01)	822 (19.44)	1579 (18.73)
Reproductive system and breast disorders	180 (4.28)	153 (3.62)	333 (3.95)
Respiratory, thoracic and mediastinal disorders	885 (21.06)	1142 (27.00)	2027 (24.04)
Skin and subcutaneous tissue disorders	290 (6.90)	303 (7.16)	593 (7.03)
Social circumstances	0 (0.00)	2 (0.05)	2 (0.02)
Surgical and medical procedures	4 (0.10)	6 (0.14)	10 (0.12)
Vascular disorders	1039 (24.72)	865 (20.45)	1904 (22.58)

Most common AEs (at least 2% of patients in any group) during the double-blind period by preferred term and treatment group (Safety set)

Preferred term	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Number of patients with at least one AE	3419 (81.35)	3503 (82.83)	6922 (82.09)
Hypotension	740 (17.61)	506 (11.97)	1246 (14.78)
Cardiac failure	730 (17.37)	832 (19.67)	1562 (18.52)
Hyperkalaemia	488 (11.61)	592 (14.00)	1080 (12.81)
Renal impairment	426 (10.14)	487 (11.52)	913 (10.83)
Cough	369 (8.78)	533 (12.60)	902 (10.70)
Dizziness	266 (6.33)	206 (4.87)	472 (5.60)
Atrial fibrillation	251 (5.97)	236 (5.58)	487 (5.78)
Pneumonia	227 (5.40)	237 (5.60)	464 (5.50)
Oedema peripheral	215 (5.12)	213 (5.04)	428 (5.08)
Dyspnoea	213 (5.07)	306 (7.24)	519 (6.16)
Nasopharyngitis	204 (4.85)	175 (4.14)	379 (4.49)
Upper respiratory tract infection	203 (4.83)	201 (4.75)	404 (4.79)
Urinary tract infection	199 (4.73)	195 (4.61)	394 (4.67)
Diarrhoea	194 (4.62)	189 (4.47)	383 (4.54)
Bronchitis	183 (4.35)	224 (5.30)	407 (4.83)
Angina pectoris	172 (4.09)	170 (4.02)	342 (4.06)
Anaemia	168 (4.00)	201 (4.75)	369 (4.38)
Back pain	164 (3.90)	138 (3.26)	302 (3.58)
Influenza	159 (3.78)	132 (3.12)	291 (3.45)
Hypokalaemia	139 (3.31)	107 (2.53)	246 (2.92)
Cardiac failure chronic	135 (3.21)	155 (3.67)	290 (3.44)
Cardiac failure congestive	133 (3.16)	167 (3.95)	300 (3.56)
Arthralgia	126 (3.00)	119 (2.81)	245 (2.91)
Hypertension	126 (3.00)	193 (4.56)	319 (3.78)
Fatigue	125 (2.97)	129 (3.05)	254 (3.01)
Diabetes mellitus	123 (2.93)	134 (3.17)	257 (3.05)
Gout	121 (2.88)	120 (2.84)	241 (2.86)
Renal failure	112 (2.66)	144 (3.41)	256 (3.04)

Preferred term	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Hyperuricaemia	108 (2.57)	151 (3.57)	259 (3.07)
Ventricular tachycardia	108 (2.57)	137 (3.24)	245 (2.91)
Noncardiac chest pain	106 (2.52)	122 (2.88)	228 (2.70)
Headache	103 (2.45)	106 (2.51)	209 (2.48)
Renal failure acute	95 (2.26)	93 (2.20)	188 (2.23)
Syncope	94 (2.24)	114 (2.70)	208 (2.47)
Chronic obstructive pulmonary disease	93 (2.21)	106 (2.51)	199 (2.36)
Insomnia	92 (2.19)	92 (2.18)	184 (2.18)
Pain in extremity	92 (2.19)	100 (2.36)	192 (2.28)
Asthenia	88 (2.09)	78 (1.84)	166 (1.97)
Nausea	88 (2.09)	100 (2.36)	188 (2.23)
Cardiac death	86 (2.05)	114 (2.70)	200 (2.37)
Constipation	86 (2.05)	124 (2.93)	210 (2.49)
Pyrexia	78 (1.86)	85 (2.01)	163 (1.93)
Cardiac failure acute	72 (1.71)	100 (2.36)	172 (2.04)
Vomiting	71 (1.69)	85 (2.01)	156 (1.85)

Adjudicated angioedema during the double-blind period by treatment group (Safety set)

		LCZ696 N=4203 n (%)		Enalapril N=4229 n (%)	
Race		Reported	Confirmed	Reported	Confirmed
All-Race	Total number of events	48	19	45	10
	Total number of patients (m)	4203 (100)	4203 (100)	4229 (100)	4229 (100)
	Number with airway compromise		0		0
	Mechanical airway protection or death from airway compromise		0		0
Black	Total number of events	8	5	3	1
	Total number of patients (m)	213 (100)	213 (100)	214 (100)	214 (100)
Non-Black	Total number of events	40	14	42	9
	Total number of patients (m)	3990 (100)	3990 (100)	4015 (100)	4015 (100)

Exposure-adjusted incidence of cognitive impairment (SMQ and NMQ) with relative risk and 95% confidence interval during the double-blind period by treatment group (Safety set)

Category	LCZ696 n/N (%) EAIR (95% CI)	Enalapril n/N (%) EAIR (95% CI)	LCZ696 vs Enalapril Relative Risk (95% CI)
Cognitive impairment –(Dementia broad SMQ)	86/4203 (2.05) 0.914 (0.731,1.129)	83/4229 (1.96) 0.889 (0.708,1.102)	1.029 (0.761,1.391)
Cognitive impairment – (Dementia narrow SMQ)	12/4203 (0.29) 0.126 (0.065,0.221)	15/4229 (0.35) 0.159 (0.089,0.263)	0.793 (0.371,1.695)

Other Relevant Findings

Not applicable

Conclusion:

The following is concluded regarding the efficacy of LCZ696 in patients with HF with NYHA functional class II to IV HF and reduced LVEF of up to 40%:

- LCZ696 is superior to enalapril in delaying the time to first occurrence of the composite of CV death or heart failure hospitalization and in reducing the risk of this endpoint by 20%.
- LCZ696 is superior to enalapril in reducing the risk of CV death alone and of heart failure hospitalization alone by 20% and 21%, respectively.
- LCZ696 is superior to enalapril in reducing the risk of all-cause mortality by 16%.
- LCZ696 results in better patient-reported quality of life with regards to maintaining higher KCCQ clinical summary scores for HF symptoms and physical limitations than enalapril.

The following is concluded regarding the safety of LCZ696 in this population:

- LCZ696 is associated with more hypotension than enalapril, but rates of discontinuation of study medication and SAEs due to this side effect are comparable between the two drugs.
- LCZ696 is associated with less renal dysfunction, less hyperkalemia, and less cough than enalapril.
- LCZ696 is associated with a higher angioedema incidence rate as compared to enalapril. Angioedema events occurring on both drugs are not severe and do not result in airway compromise. Angioedema occurs in black patients more frequently than in non-black patients. Also, the rate of angioedema incidence among blacks on LCZ696 is higher than on enalapril.
- LCZ696 and enalapril are associated with similar rates of dementia-related AEs.
- LCZ696 and enalapril are associated with comparable rates of gastric lesions, hypersensitivity reactions (including pruritus), changes in bone growth/mineral density, stimulation of lipolysis, cancer promotion, QT wave prolongation, developmental toxicity, and hepatotoxicity.

Based on the results of the PARADIGM-HF study (CLCZ696B2314), LCZ696 has been demonstrated to be safe and effective in reducing morbidity and mortality in NYHA functional class II to IV HF patients with LVEF of up to 40%, and has been shown to be superior to enalapril in reducing the risks of CV death, of all-cause mortality and of hospitalization for HF and decreasing the symptoms and physical limitations of HF.

Date of Clinical Trial Report

05 December 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

21 May 2015

Date of Latest Update

Reason for Update