Clinical trial results:
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

Summary

EudraCT number	2013-001835-33
Trial protocol	HU IT SK ES DE FI GB BG
Global end of trial date	05 August 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	CLCZ696B2228

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01922089
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,

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	05 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

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	15 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 42
Country: Number of subjects enrolled	Germany: 83
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Hungary: 49
Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Slovakia: 80
Country: Number of subjects enrolled	Turkey: 25
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 67
Worldwide total number of subjects	498
EEA total number of subjects	406

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)	250
From 65 to 84 years	241
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were stratified based on the level of RAAS inhibition; High RAAS stratum and Low RAAS stratum.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696 Condensed

Arm description:

Up-titration to LCZ696 200 mg twice daily (bid) over 3 weeks

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	LCZ696
Other name	Sacubitril/valsartan
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Up-titration to LCZ696 200 mg twice daily (bid) over 3 weeks

Arm title	LCZ696 Conservative

Arm description:

Up-titration to LCZ696 200 mg bid over 6 weeks

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	LCZ696
Other name	Sacubitril/valsartan
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Up-titration to LCZ696 200 mg twice daily (bid) over 6bweeks

Number of subjects in period 1	LCZ696 Condensed	LCZ696 Conservative
Started	247	251
Safety Set	246	251
Completed	208	221
Not completed	39	30

Adverse event, serious fatal	2	1
Consent withdrawn by subject	3	4
Physician decision	2	3
Adverse event, non-fatal	18	13
Protocol Deviation	10	7
administrative problems	4	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	LCZ696 Condensed
Reporting group description: Up-titration to LCZ696 200 mg twice daily (bid) over 3 weeks	
Reporting group title	LCZ696 Conservative
Reporting group description: Up-titration to LCZ696 200 mg bid over 6 weeks	

Reporting group values	LCZ696 Condensed	LCZ696 Conservative	Total
Number of subjects	247	251	498
Age categorical Units: Subjects			
Age Continuous | Units: years			
arithmetic mean	64.2	63.8	
standard deviation	± 11.86	± 10.94	-
Gender, Male/Female Units: participants			
Male	191	201	392
Female	56	50	106

End points

End points reporting groups

Reporting group title	LCZ696 Condensed
Reporting group description:	
Up-titration to LCZ696 200 mg twice daily (bid) over 3 weeks	
Reporting group title	LCZ696 Conservative
Reporting group description:	
Up-titration to LCZ696 200 mg bid over 6 weeks	

Primary: Number of participants experiencing hypotension, renal dysfunction, hyperkalemia and angioedema and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low)

End point title	Number of participants experiencing hypotension, renal dysfunction, hyperkalemia and angioedema and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low)[1]

End point description:

Participants experiencing hypotension, renal dysfunction, hyperkalemia and angioedema and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low) High RAAS stratum Patients receiving > 160 mg of valsartan or > 10 mg total daily dose of enalapril, or equivalent doses of other ARBs/ACEIs, respectively, at screening Low RAAS stratum: Patients receiving ≤ 160 mg of valsartan or ≤ 10 mg total daily dose of enalapril, or equivalent doses of other ARBs/ACEIs, respectively, at screening. This stratum also included patients who were not on an ACEI or an ARB 4 weeks prior to screening (i.e., ACEI/ARB-naïve patients) "No statistical analysis was planned for this primary outcome."

End point type	Primary

End point timeframe:

12 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this endpoint.

End point values	LCZ696 Condensed	LCZ696 Conservative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	251		
Units: participants				
Hypotension High RAAS (n=120, 127)	5	7		
Hypotension Low RAAS (n=127, 124)	19	14		
Hypotension ALL	24	21		
Renal Dysfunction High RAAS (n=120, 127)	5	9		
Renal Dysfunction Low RAAS (n=127, 124)	13	10		
Renal Dysfunction ALL	18	19		
Hyperkalemia High RAAS (n=120, 127)	8	5		
Hyperkalemia Low RAAS (n=127, 124)	11	6		
Hyperkalemia ALL	19	11		
Angioedema High RAAS (n=120, 127)	0	1		
Angioedema Low RAAS (n=127, 124)	0	1		
Angioedema ALL	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved treatment success over the 12 weeks and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low)

End point title	Number of participants who achieved treatment success over the 12 weeks and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low)

End point description:

Treatment success was defined as the proportion of patients who achieved and maintained LCZ696 200 mg bid without any dose interruption or down-titration over 12 weeks and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low) High RAAS stratum Patients receiving > 160 mg of valsartan or > 10 mg total daily dose of enalapril, or equivalent doses of other ARBs/ACEIs, respectively, at screening Low RAAS stratum: Patients receiving ≤ 160 mg of valsartan or ≤ 10 mg total daily dose of enalapril, or equivalent doses of other ARBs/ACEIs, respectively, at screening. This stratum also included patients who were not on an ACEI or an ARB 4 weeks prior to screening (i.e., ACEI/ARB-naïve patients)

End point type	Secondary

End point timeframe:

12 weeks

End point values	LCZ696 Condensed	LCZ696 Conservative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	251		
Units: participants				
High RAAS (n=109,117)	90	98		
Low RAAS (n=121,119)	89	101		
ALL (n=230,236)	179	199		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who tolerated study medication for at least the last two weeks of the study and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low).

End point title	Number of participants who tolerated study medication for at least the last two weeks of the study and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low).

End point description:

Tolerability was assessed as the proportion of patients who achieved LCZ696 200 mg bid and

maintained this dose for at least 2 weeks before study completion, regardless of previous dose interruption or down-titration and by Renin-Angiotensin-Aldosterone System (RAAS) stratum (high vs. low) High RAAS stratum Patients receiving > 160 mg of valsartan or > 10 mg total daily dose of enalapril, or equivalent doses of other ARBs/ACEIs, respectively, at screening Low RAAS stratum: Patients receiving ≤ 160 mg of valsartan or ≤ 10 mg total daily dose of enalapril, or equivalent doses of other ARBs/ACEIs, respectively, at screening. This stratum also included patients who were not on an ACEI or an ARB 4 weeks prior to screening (i.e., ACEI/ARB-naïve patients)

End point type	Secondary

End point timeframe:

12 weeks

End point values	LCZ696 Condensed	LCZ696 Conservative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	251		
Units: participants				
High RAAS (n=109,117)	94	103		
Low RAAS (n=121,119)	97	103		
ALL (n=230,236)	191	206		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	LCZ696 Conservative

Reporting group description:

Up-titration to LCZ696 200 mg bid over 6 weeks

Reporting group title	LCZ696 Condensed

Reporting group description:

Up-titration to LCZ696 200 mg twice daily (bid) over 3 weeks

Serious adverse events	LCZ696 Conservative	LCZ696 Condensed	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 251 (5.58%)	21 / 246 (8.54%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac death			

subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 251 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 251 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 251 (0.80%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 251 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac ventricular thrombosis			

subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 251 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 251 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure acute			
subjects affected / exposed	0 / 251 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LCZ696 Conservative	LCZ696 Condensed	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 251 (12.35%)	39 / 246 (15.85%)	
Vascular disorders			
Hypotension			

subjects affected / exposed occurrences (all)	21 / 251 (8.37%) 21	24 / 246 (9.76%) 24	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	11 / 251 (4.38%) 15	16 / 246 (6.50%) 17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2014	The main purpose of this amendment is to align study exclusion criteria 30 from study protocol CLCZ696B2228 with the exclusion criteria of the other study protocols from the LCZ696 clinical program and with the LCZ696 Investigators' Brochure. The Novartis standard protocol template language requires contraception use during study medication dosing and until 5 times the terminal half-life of the study drug has elapsed following the final dose. At the end of this period, the concentration of the compound in the blood will be very low and the drug is considered eliminated. According to the current Novartis protocol template, the longest t1/2, for LBQ657, would require contraception to continue for 4 days after the last dose of study medication. Therefore, even if the mean half-life indicates that contraception for 4 days following the last dose of study medication is considered sufficient, the contraception period for women of child-bearing potential after being taken off study medication is changed to ensure consistency with other studies and documents from 4 days to 7 days. Additionally, due to changes in the timing of the study, there was no significant data for the LCZ696B2228 study to be specifically reviewed by the DMC at the March 28, 2014 DMC meeting. As a consequence the DMC review plan is adjusted to match with the current study progress.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported