Clinical trial results:
A randomized, double-blind 52-week study to evaluate the safety and efficacy of an LCZ696 regimen compared to an olmesartan regimen on arterial stiffness through assessment of central blood pressure in elderly patients with hypertension

Summary

EudraCT number	2012-002899-14
Trial protocol	IT GR ES
Global end of trial date	08 April 2015

Results information

Result version number	v1 (current)
This version publication date	16 April 2016
First version publication date	16 April 2016

Trial information

Trial identification

Sponsor protocol code	CLCZ696A2216

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01692301
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, trialandresults.registries@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, trialandresults.registries@novartis.com

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	08 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of an LCZ696 regimen compared to an olmesartan regimen, as measured by change from baseline in mean CASP after 12 weeks of treatment in elderly patients with essential hypertension.

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.
Rescue medication (amlodipine or HCTZ) was allowed for patients whose BP was not controlled (msSBP ≥140 mmHg or msDBP ≥90 mmHg) after at least 8 weeks of treatment with LCZ696 400 mg or olmesartan 40 mg. Open-label amlodipine (2.5-5 mg) and then HCTZ (6.25-25 mg) was added at intervals of 4 weeks from Week 12 to Week 24.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2012
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	Argentina: 76
Country: Number of subjects enrolled	Colombia: 12
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Greece: 24
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Korea, Republic of: 33
Country: Number of subjects enrolled	Russian Federation: 66
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	United States: 112
Worldwide total number of subjects	454
EEA total number of subjects	128

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)	154
From 65 to 84 years	296
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

454 patients were randomized to the 12-week double-blind epoch to receive LCZ696 or olmesartan

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696 (sacubitril/valsartan)

Arm description:

Randomized patients received LCZ696 once daily for four weeks, then they force-titrated to a higher dose at Week 4 and stayed on this dose of LCZ696 once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double-blind design, 2 tablets (LCZ696, its matching placebo) and 1 capsule (olmesartan matching placebo) were given during the entire study.

Arm type	Experimental
Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg or 200 mg tablet

Investigational medicinal product name	Olmesartan matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Olmesartan matching placebo 20 mg and 40 mg capsules

Investigational medicinal product name	amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

amlodipine 2.5 mg or 5 mg tablets

Investigational medicinal product name	Hydrochlorothiazide
Investigational medicinal product code	HCTZ
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Hydrochlorothiazide 6.25mg, 12.5mg, or 25 mg tablets

Arm title	Olmesartan

Arm description:

Randomized patients received olmesartan once daily for four weeks, then force-titrated to a higher dose at Week 4 and stayed on this dose of olmesartan once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double-blind design, 2 tablets (LCZ696 matching placebo) and 1 capsule (olmesartan) were given during the entire study.

Arm type	Active comparator
Investigational medicinal product name	Olmesartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg and 40 mg capsules

Investigational medicinal product name	LCZ696 matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LCZ696 Matching Placebo of 100 mg or 200 mg tablet

Investigational medicinal product name	amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

amlodipine 2.5 mg or 5 mg tablets

Investigational medicinal product name	Hydrochlorothiazide
Investigational medicinal product code	HCTZ
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Hydrochlorothiazide 6.25mg, 12.5mg, or 25 mg tablets

Number of subjects in period 1	LCZ696 (sacubitril/valsartan)	Olmesartan
Started	229	225
Completed	184	183
Not completed	45	42
Adverse event, serious fatal	1	2

Physician decision	2	2
Adverse event, non-fatal	15	12
Technical problems	-	1
Non-compliance with study treatment	1	2
Protocol deviation	9	2
Patient/guardian decision	16	15
Lost to follow-up	1	1
Lack of efficacy	-	5

Baseline characteristics

Reporting groups	
Reporting group title	LCZ696 (sacubitril/valsartan)
Reporting group description:	
Randomized patients received LCZ696 once daily for four weeks, then they force-titrated to a higher dose at Week 4 and stayed on this dose of LCZ696 once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double-blind design, 2 tablets (LCZ696, its matching placebo) and 1 capsule (olmesartan matching placebo) were given during the entire study.	
Reporting group title	Olmesartan
Reporting group description:	
Randomized patients received olmesartan once daily for four weeks, then force-titrated to a higher dose at Week 4 and stayed on this dose of olmesartan once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double-blind design, 2 tablets (LCZ696 matching placebo) and 1 capsule (olmesartan) were given during the entire study.	

Reporting group values	LCZ696 (sacubitril/valsartan)	Olmesartan	Total
Number of subjects	229	225	454
Age categorical Units: Subjects			
Adults (18-64 years)	67	87	154
From 65-84 years	161	135	296
85 years and over	1	3	4
Age Continuous | Units: Years			
arithmetic mean	68.2	67.2	
standard deviation	± 5.73	± 5.97	-
Gender, Male/Female Units: Participants			
Female	110	107	217
Male	119	118	237

End points

End points reporting groups

Reporting group title	LCZ696 (sacubitril/valsartan)

Reporting group description:

Randomized patients received LCZ696 once daily for four weeks, then they force-titrated to a higher dose at Week 4 and stayed on this dose of LCZ696 once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double-blind design, 2 tablets (LCZ696, its matching placebo) and 1 capsule (olmesartan matching placebo) were given during the entire study.

Reporting group title	Olmesartan

Reporting group description:

Randomized patients received olmesartan once daily for four weeks, then force-titrated to a higher dose at Week 4 and stayed on this dose of olmesartan once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double-blind design, 2 tablets (LCZ696 matching placebo) and 1 capsule (olmesartan) were given during the entire study.

Primary: Change from baseline in mean central aortic systolic pressure (CASP) at 12 weeks

End point title	Change from baseline in mean central aortic systolic pressure (CASP) at 12 weeks

End point description:

Central aortic blood pressure was derived from peripheral pressure waveforms recorded noninvasively from the brachial artery using a cuff-based device. This technique uses the brachial pressure and a signal processing algorithm to transform brachial signals into central blood pressure (BP) waveforms. When the aortic pressure waveform was derived, key pulse wave analysis (PWA) parameters, such as CASP was calculated by the system software. At the first study visit, the arm with the highest systolic blood pressure (SBP) was used for all subsequent PWA. Brachial PWA measurements were performed on the same arm that the office blood pressures were taken. Two pulse waveform measurements, meeting all quality control criteria were captured at baseline and at week 12 visits.

End point type	Primary

End point timeframe:

baseline, 12 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	206		
Units: mmHg				
least squares mean (standard error)	-12.57 (± 1.01)	-8.9 (± 1.01)		

Statistical analyses

Statistical analysis title	Change from baseline treatment difference in group
Comparison groups	LCZ696 (sacubitril/valsartan) v Olmesartan
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.45
upper limit	-0.87
Variability estimate	Standard error of the mean
Dispersion value	1.42

Secondary: Change from baseline in mean central pulse (CPP) pressure

End point title	Change from baseline in mean central pulse (CPP) pressure

End point description:

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to Week 12 (n = 207, 206)	-6.41 (± 0.69)	-3.96 (± 0.69)		
Baseline to Week 52 (n = 209, 208)	-7.16 (± 0.69)	-6.65 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean pulse wave velocity (PWV)

End point title	Change from baseline in mean pulse wave velocity (PWV)

End point description:

Pulse wave velocity recordings were performed on patient while in a supine, face-up position. Tonometry was performed on the carotid simultaneously with the cuff inflation over the femoral artery. Two pulse

wave velocity measures, meeting all quality control criteria were captured at baseline, week 12 and week 52.

End point type	Secondary

End point timeframe:

baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: meter/second				
least squares mean (standard error)				
Baseline to week 12 (n= 192, 196)	-0.68 (± 0.12)	-0.57 (± 0.12)		
Baseline to week 52 (n= 199, 199)	-0.83 (± 0.13)	0.77 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean central aortic systolic pressure (CASP) at 52 weeks

End point title	Change from baseline in mean central aortic systolic pressure (CASP) at 52 weeks

End point description:

Central aortic blood pressure was derived from peripheral pressure waveforms recorded noninvasively from the brachial artery using a cuff-based device. This technique uses the brachial pressure and a signal processing algorithm to transform brachial signals into central blood pressure (BP) waveforms. When the aortic pressure waveform was derived, key pulse wave analysis (PWA) parameters, such as CASP was calculated by the system software. At the first study visit, the arm with the highest systolic blood pressure (SBP) was used for all subsequent PWA. Brachial PWA measurements were performed on the same arm that the office blood pressures were taken. Two pulse waveform measurements, meeting all quality control criteria were captured at baseline and at week 12 visits.

End point type	Secondary

End point timeframe:

baseline, 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	208		
Units: mmHg				
least squares mean (standard error)	-16.18 (± 0.96)	-14.7 (± 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean sitting systolic blood pressure (msSBP)

End point title	Change from baseline in mean sitting systolic blood pressure (msSBP)

End point description:

At the first study visit, the patient had his/her blood pressure (BP) measured in both arms; the arm in which the highest sitting SBP was found was used for all subsequent readings throughout the study. At each study visit, after the patient had been sitting for 5 minutes, SBP were measured 3 times using a standard mercury sphygmomanometer and appropriate size cuff. The repeat sitting measurements were made at 1- to 2-minute intervals and the mean of those 3 measurements was used as the average sitting office BP for that visit.

End point type	Secondary

End point timeframe:

baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to week 12 (n=226, 222)	-20.84 (± 1.06)	-14.57 (± 1.07)		
Baseline to week 52 (n=226,223)	-23.91 (± 0.98)	-21.45 (± 0.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean sitting diastolic blood pressure (msDBP)

End point title	Change from baseline in mean sitting diastolic blood pressure (msDBP)

End point description:

At the first study visit, the patient had his/her blood pressure (BP) measured in both arms; the arm in which the highest sitting SBP was found was used for all subsequent readings throughout the study. At each study visit, after the patient had been sitting for 5 minutes, DBP were measured 3 times using a standard mercury sphygmomanometer and appropriate size cuff. The repeat sitting measurements were made at 1- to 2-minute intervals and the mean of those 3 measurements was used as the average sitting office BP for that visit.

End point type	Secondary

End point timeframe:

baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to week 12 (n=226, 222)	-7.86 (± 0.58)	-5.58 (± 0.59)		
Baseline to week 52 (n=226,223)	-8.92 (± 0.57)	-7.85 (± 0.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean sitting pulse pressure (msPP)

End point title	Change from baseline in mean sitting pulse pressure (msPP)

End point description:

Mean sitting pulse pressure for each patient and visit was calculated as the difference between the calculated values of mean sitting systolic blood pressure and mean sitting diastolic blood pressure.

End point type	Secondary

End point timeframe:

baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to week 12 (n=226,222)	-13.13 (± 0.82)	-8.86 (± 0.82)		
Baseline to week 52 (n= 226, 223)	-15.02 (± 0.79)	-13.58 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean arterial pressure (MAP)

End point title	Change from baseline in mean arterial pressure (MAP)

End point description:

Mean arterial pressure (MAP) was calculated from mean sitting systolic BP (msSBP) and mean sitting diastolic BP (msDBP) as (2 * msDBP + msSBP)/3.

End point type	Secondary

End point timeframe:

baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to week 12 (n=226, 222)	-12.19 (± 0.68)	-8.57 (± 0.68)		
Baseline to week 52 (n=226, 223)	-13.92 (± 0.63)	-12.38 (± 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean 24-hour systolic blood pressure (maSBP)

End point title	Change from baseline in mean 24-hour systolic blood pressure (maSBP)

End point description:

An Ambulatory Blood Pressure Monitor (ABPM) measured a participant's blood pressure over a 24 hour period using an automated validated monitoring device at baseline, week 12 and at week 52 starting one day before each visit. The 24 hour maSBP was calculated by taking the mean of all ambulatory systolic blood pressure readings for the 24 hour period.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to week 12 (n= 164, 162)	-13.25 (± 0.62)	-9.14 (± 0.62)		

Baseline to week 52 (n= 174, 176)	-14.15 (± 0.59)	-14.32 (± 0.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean 24-hour diastolic blood pressure (maDBP)

End point title	Change from baseline in mean 24-hour diastolic blood pressure (maDBP)

End point description:

An Ambulatory Blood Pressure Monitor (ABPM) measured a participant's blood pressure over a 24 hour period using an automated validated monitoring device at baseline, week 12 and at week 52 starting one day before each visit. The 24 hour maDBP was calculated by taking the mean of all ambulatory systolic blood pressure readings for the 24 hour period.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to week 12 (n= 164, 162)	-7.44 (± 0.37)	-5.48 (± 0.36)		
Baseline to week 52 (n= 174, 176)	-8.85 (± 0.35)	-8.44 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean 24-hour ambulatory pulse pressure (maPP)

End point title	Change from baseline in mean 24-hour ambulatory pulse pressure (maPP)

End point description:

Mean 24 hour ambulatory pulse pressure was calculated as the difference between the mean 24 hour systolic and diastolic ambulatory blood pressure in corresponding visits i.e. baseline, week 12 and week 52.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, and 52 weeks

End point values	LCZ696 (sacubitril/valsartan)	Olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	225		
Units: mmHg				
least squares mean (standard error)				
Baseline to Week 12 (n=164, 162)	-5.77 (± 0.35)	-3.69 (± 0.35)		
Baseline to week 52 (n=174, 176)	-5.26 (± 0.36)	-5.91 (± 0.35)		

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 are reported in this record from 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	18.0

Reporting groups

Reporting group title	LCZ696 (sacubitril/valsartan)

Reporting group description:

Randomized patients received LCZ696 once daily for four weeks, then they force-titrated to a higher dose at Week 4 and stayed on this dose of LCZ696 once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double blind design, 2 tablets (LCZ696, its matching placebo) and 1 capsule (olmesartan matching placebo) were given during the entire study.

Reporting group title	Olmesartan

Reporting group description:

Randomized patients received olmesartan once daily for four weeks, then force-titrated to a higher dose at Week 4 and stayed on this dose of olmesartan once daily for the remainder of the treatment period. At week 12, patients with uncontrolled BP allowed to have amlodipine then hydrochlorothiazide (HCTZ) added at intervals of 4 weeks from Week 12 up to Week 24. To maintain the double dummy, double blind design, 2 tablets (LCZ696 matching placebo) and 1 capsule (olmesartan) were given during the entire study.

Serious adverse events	LCZ696 (sacubitril/valsartan)	Olmesartan	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 229 (6.99%)	13 / 225 (5.78%)	
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)			
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSIVE CRISIS			

subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PULMONARY PNEUMATOCELE			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
BLOOD PRESSURE INCREASED			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
HIP FRACTURE			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY CONTUSION			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	0 / 229 (0.00%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TENDON RUPTURE			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

VASCULAR GRAFT OCCLUSION			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (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 CORONARY SYNDROME			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA PECTORIS			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 229 (0.87%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			

subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
BRAIN STEM INFARCTION			
subjects affected / exposed	0 / 229 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COAGULOPATHY			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CATARACT			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
INGUINAL HERNIA			

subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS CHRONIC			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
OSTEOCHONDROSIS			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DOUGLAS' ABSCESS			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	1 / 229 (0.44%)	0 / 225 (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: 2 %

Non-serious adverse events	LCZ696 (sacubitril/valsartan)	Olmesartan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 229 (31.88%)	55 / 225 (24.44%)	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	2 / 229 (0.87%)	5 / 225 (2.22%)	
occurrences (all)	2	6	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	12 / 229 (5.24%)	12 / 225 (5.33%)	
occurrences (all)	15	15	
HEADACHE			
subjects affected / exposed	14 / 229 (6.11%)	10 / 225 (4.44%)	
occurrences (all)	15	13	
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	6 / 229 (2.62%)	2 / 225 (0.89%)	
occurrences (all)	6	2	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	6 / 229 (2.62%)	5 / 225 (2.22%)	
occurrences (all)	7	8	
ABDOMINAL PAIN			
subjects affected / exposed	5 / 229 (2.18%)	1 / 225 (0.44%)	
occurrences (all)	7	1	
NAUSEA			
subjects affected / exposed	5 / 229 (2.18%)	2 / 225 (0.89%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	10 / 229 (4.37%)	2 / 225 (0.89%)	
occurrences (all)	13	2	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	5 / 229 (2.18%)	7 / 225 (3.11%)	
occurrences (all)	7	8	

BACK PAIN			
subjects affected / exposed	3 / 229 (1.31%)	10 / 225 (4.44%)	
occurrences (all)	3	11	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	16 / 229 (6.99%)	12 / 225 (5.33%)	
occurrences (all)	24	16	
INFLUENZA			
subjects affected / exposed	7 / 229 (3.06%)	5 / 225 (2.22%)	
occurrences (all)	8	5	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	6 / 229 (2.62%)	6 / 225 (2.67%)	
occurrences (all)	7	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2014	The primary purpose of protocol amendment to remove all references to an interim 12 week database lock. The 12 week primary analysis of the study was conducted at the end of the full 52 week study period. Corrections and inconsistencies in the protocol were also implemented with this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported