Clinical trial results:
A randomized, double-blind, active-controlled, parallel group, 52-week study to evaluate the effect of LCZ696 compared to olmesartan on regional aortic stiffness in subjects with essential hypertension

Summary

EudraCT number	2012-005720-15
Trial protocol	GB DE
Global end of trial date	04 June 2015

Results information

Result version number	v1 (current)
This version publication date	17 June 2016
First version publication date	17 June 2016

Trial information

Trial identification

Sponsor protocol code	CLCZ696A2224

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01870739
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	04 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of LCZ696 based treatment regimen as compared to olmesartan on local aortic distensibility as measured by MRI after 52 weeks of treatment in hypertensive patients

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	02 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 91
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Switzerland: 21
Worldwide total number of subjects	114
EEA total number of subjects	93

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)	76

From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 115 patients were enrolled. One patient was discontinued after randomization before receiving any dose of study randomized medication.
A total of 114 patients received study randomized medication

Period 1

Period 1 title	Single Drug treatment (12 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

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

Arm description:

LCZ696 based treatment strategy (LCZ696 200 mg for 2 weeks as initiation dose, LCZ696 400 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)

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:

200 mg tablets

Investigational medicinal product name	Amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2.5 mg, 5 mg, and 10 mg once daily

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

Dosage and administration details:

matching placebo of olmesartan

Arm title	olmesartan

Arm description:

Olmesartan based treatment strategy (olmesartan 20 mg for 2 weeks as initiation dose, olmesartan 40 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)

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: Olmesartan 20 mg capsule	
Investigational medicinal product name	Amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2.5 mg, 5 mg, and 10 mg once daily	
Investigational medicinal product name	placebo of sacubitril/valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: matching placebo of sacubitril/valsartan	

Number of subjects in period 1	sacubitril/valsartan (LCZ696)	olmesartan
Started	57	57
Initiation Dose completed	57	56
Maintenance Dose started	57	56
Completed	54	53
Not completed	3	4
Adverse event, non-fatal	-	1
Protocol deviation	-	1
Administrative problems	3	2

Period 2	
Period 2 title	Add-on Period (40 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor
Arms	
Are arms mutually exclusive?	Yes

Arm title	sacubitril/valsartan (LCZ696)

Arm description:

LCZ696 based treatment strategy (LCZ696 200 mg for 2 weeks as initiation dose, LCZ696 400 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)

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:

200 mg tablets

Investigational medicinal product name	Amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2.5 mg, 5 mg, and 10 mg once daily

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

Dosage and administration details:

matching placebo of olmesartan

Arm title	olmesartan

Arm description:

Olmesartan based treatment strategy (olmesartan 20 mg for 2 weeks as initiation dose, olmesartan 40 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)

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:

Olmesartan 20 mg capsule

Investigational medicinal product name	placebo of sacubitril/valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

matching placebo of sacubitril/valsartan

Investigational medicinal product name	Amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
2.5 mg, 5 mg, and 10 mg once daily

Number of subjects in period 2	sacubitril/valsartan (LCZ696)	olmesartan
Started	54	53
Completed	51	51
Not completed	3	2
Patient withdrew consent	1	-
Adverse event, non-fatal	-	1
Unsatisfactory therapeutic effect	1	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	sacubitril/valsartan (LCZ696)
Reporting group description:	
LCZ696 based treatment strategy (LCZ696 200 mg for 2 weeks as initiation dose, LCZ696 400 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)	
Reporting group title	olmesartan
Reporting group description:	
Olmesartan based treatment strategy (olmesartan 20 mg for 2 weeks as initiation dose, olmesartan 40 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)	

Reporting group values	sacubitril/valsartan (LCZ696)	olmesartan	Total
Number of subjects	57	57	114
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: Years			
arithmetic mean	60.5	59.2	
standard deviation	± 7.8	± 13.1	-
Gender, Male/Female Units: Participants			
Female	20	17	37
Male	37	40	77

End points

End points reporting groups

Reporting group title	sacubitril/valsartan (LCZ696)
Reporting group description:	
LCZ696 based treatment strategy (LCZ696 200 mg for 2 weeks as initiation dose, LCZ696 400 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)	
Reporting group title	olmesartan
Reporting group description:	
Olmesartan based treatment strategy (olmesartan 20 mg for 2 weeks as initiation dose, olmesartan 40 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)	
Reporting group title	sacubitril/valsartan (LCZ696)
Reporting group description:	
LCZ696 based treatment strategy (LCZ696 200 mg for 2 weeks as initiation dose, LCZ696 400 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)	
Reporting group title	olmesartan
Reporting group description:	
Olmesartan based treatment strategy (olmesartan 20 mg for 2 weeks as initiation dose, olmesartan 40 mg for additional 50 weeks as maintenance dose. Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target)	
Subject analysis set title	Initiation dose : sacubitril/valsartan (LCZ696 200mg)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients received LCZ696 200 mg for 2 weeks as initiation dose for 2 weeks	
Subject analysis set title	Initiation dose: olmesartan 20mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients received olmesartan 20 mg for 2 weeks as initiation dose for 2 weeks	
Subject analysis set title	Maintenance Dose: sacubitril/valsartan (LCZ696 400mg)
Subject analysis set type	Full analysis
Subject analysis set description:	
After 2 weeks on initiation dose, patients were dosed at the maintenance dose level of LCZ696 400 mg for 10 weeks	
Subject analysis set title	Maintenance Dose: olmesartan 40 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
After 2 weeks on initiation dose, patients were dosed at the maintenance dose level of olmesartan 40 mg for 10 weeks	
Subject analysis set title	Sacubitril/valsartan (LCZ696 400mg) +/- Amlodipine
Subject analysis set type	Full analysis
Subject analysis set description:	
Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target	
Subject analysis set title	Olmesartan 40mg +/- Amlodipine
Subject analysis set type	Full analysis
Subject analysis set description:	
Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target	

Primary: Change from baseline in ascending aorta distensibility at 52 week

End point title	Change from baseline in ascending aorta distensibility at 52 week

End point description:

Cardiovascular magnetic resonance imaging (MRI) scans were obtained at baseline prior to randomization, at week 52 for the assessment of local aortic distensibility. Ascending aorta distensibility was one of the 3 components for measuring local arota distensibility.

End point type	Primary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: 10^(-3) x mmHg^(-1)				
least squares mean (standard error)	0.269 (± 0.1283)	0.33 (± 0.1233)		

Statistical analyses

Statistical analysis title	Treatment diff. in Ascending Aorta Distensibility
Comparison groups	sacubitril/valsartan (LCZ696) v olmesartan
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7324
Method	Linear Model
Parameter estimate	Mean difference (net)
Point estimate	-0.0616
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4178
upper limit	0.2947

Primary: Change from baseline in proximal descending aorta distensibility at 52 weeks

End point title	Change from baseline in proximal descending aorta distensibility at 52 weeks

End point description:

Cardiovascular magnetic resonance imaging (MRI) scans were obtained at baseline prior to randomization, at week 52 for the assessment of local aortic distensibility. Proximal descending aorta distensibility was one of the 3 components for measuring local arota distensibility.

End point type	Primary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: 10^(-3) x mmHg^(-1)				
least squares mean (standard error)	0.51 (± 0.1528)	0.547 (± 0.1469)		

Statistical analyses

Statistical analysis title	Treatment diff. in Proximal Descending Aorta
Comparison groups	sacubitril/valsartan (LCZ696) v olmesartan
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8614
Method	Linear Model
Parameter estimate	Mean difference (net)
Point estimate	-0.0371
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4582
upper limit	0.3839

Primary: Change from baseline in distal descending aorta distensibility at 52 weeks

End point title	Change from baseline in distal descending aorta distensibility at 52 weeks

End point description:

Cardiovascular magnetic resonance imaging (MRI) scans were obtained at baseline prior to randomization, at week 52 for the assessment of local aortic distensibility. Distal descending aorta distensibility was one of the 3 components for measuring local arota distensibility.

End point type	Primary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: 10^(-3) x mmHg^(-1)				
least squares mean (standard error)	0.417 (± 0.2242)	0.498 (± 0.2156)		

Statistical analyses

Statistical analysis title	Treatment diff. in distal descending aorta
Comparison groups	sacubitril/valsartan (LCZ696) v olmesartan
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7946
Method	Linear Model
Parameter estimate	Mean difference (net)
Point estimate	-0.0812
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6987
upper limit	0.5362

Secondary: Change from baseline in local aortic strain at 52 weeks

End point title	Change from baseline in local aortic strain at 52 weeks

End point description:

Cardiovascular magnetic resonance imaging (MRI) scans were obtained at baseline prior to randomization, at week 52 for the assessment of local aortic strain. Local aortic strain was measured by assessing ascending aorta strain, proximal descending aorta strain and distal descending aorta strain.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: percentage of change in aorta strain				
least squares mean (standard error)				
Ascending Aorta Strain	-0.83 (± 0.7903)	0.453 (± 0.7598)		
Proximal Descending Aorta Strain	-0.284 (± 0.894)	-0.066 (± 0.8596)		

Distal Descending Aorta Strain	-1.092 (± 1.0956)	0.225 (± 1.0533)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in regional aortic pulse wave velocity at 52 weeks

End point title	Change from baseline in regional aortic pulse wave velocity at 52 weeks

End point description:

Cardiovascular magnetic resonance imaging (MRI) scans were obtained at baseline prior to randomization, at week 52 for the assessment of regional aortic pulse wave velocity.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: meters per second (m/s)				
least squares mean (standard error)	-2.086 (± 0.5029)	-1.085 (± 0.4835)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Central blood pressure at 52 weeks

End point title	Change from baseline in Central blood pressure at 52 weeks

End point description:

Central blood pressure was determined by measuring central systolic blood pressure , diastolic blood pressure and pulse pressure.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: mmHg				
least squares mean (standard error)				
Central systolic blood pressure	-16.655 (± 1.4968)	-13.625 (± 1.4968)		
Central diastolic blood pressure	-10.318 (± 1.0578)	-10.432 (± 1.0578)		
Central pulse pressure	-6.539 (± 0.9428)	-3.041 (± 0.9428)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in augmentation pressure at 52 weeks

End point title	Change from baseline in augmentation pressure at 52 weeks

End point description:

Augmentation pressure is the added pressure during systole due to wave reflection.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: mmHg				
least squares mean (standard error)	-2.443 (± 0.595)	-1.437 (± 0.595)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in augmentation index at 52 weeks

End point title	Change from baseline in augmentation index at 52 weeks

End point description:

Augmentation index (AIx) is the percentage of the central pulse pressure due to wave reflection.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: percentage of change in Alx				
least squares mean (standard error)	-2.385 (± 1.1805)	-1.515 (± 1.1805)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in carotid-femoral pulse wave velocity at 52 weeks

End point title	Change from baseline in carotid-femoral pulse wave velocity at 52 weeks

End point description:

For pulse wave velocity calculation, the pressure waveform at the femoral site (using a partially inflated custom blood pressure cuff) and the carotid site (using hand -held applanation tonometry) were measured simultaneously. Pulse wave analysis was performed on the central aortic pressure waveform as derived from the brachial pressure waveform recorded in a partially-inflated blood pressure cuff around the upper arm.

End point type	Secondary

End point timeframe:

Baseline, 52 weeks

End point values	sacubitril/valsartan (LCZ696)	olmesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: meters per second (m/s)				
least squares mean (standard error)	-0.428 (± 0.1663)	-0.434 (± 0.1663)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with reported adverse events, serious adverse events and death

End point title	Number of patients with reported adverse events, serious adverse events and death

End point description:

This outcome measure summarizes patients with any adverse events, serious adverse events and death.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Initiation dose : sacubitril/valsartan (LCZ696 200mg)	Initiation dose: olmesartan 20mg	Maintenance Dose: sacubitril/valsartan (LCZ696 400mg)	Maintenance Dose: olmesartan 40 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	57	57	56
Units: Patients				
Any Adverse events	13	16	21	28
Serious Adverse Events	0	2	0	2
Death	0	0	0	0

End point values	Sacubitril/valsartan (LCZ696 400mg) +/- Amlodipine	Olmesartan 40mg +/- Amlodipine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	53		
Units: Patients				
Any Adverse events	31	38		
Serious Adverse Events	6	5		
Death	0	0		

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Initiation dose : sacubitril/valsartan (LCZ696 200mg)

Reporting group description:

Patients received LCZ696 200 mg for 2 weeks as initiation dose for 2 weeks

Reporting group title	Initiation dose: olmesartan 20mg

Reporting group description:

Patients received olmesartan 20 mg for 2 weeks as initiation dose for 2 weeks

Reporting group title	Maintenance Dose: sacubitril/valsartan (LCZ696 400mg)

Reporting group description:

After 2 weeks on initiation dose, patients were dosed at the maintenance dose level of LCZ696 400 mg for 10 weeks

Reporting group title	Maintenance Dose: olmesartan 40 mg

Reporting group description:

After 2 weeks on initiation dose, patients were dosed at the maintenance dose level of olmesartan 40 mg for 10 weeks

Reporting group title	Sacubitril/valsartan (LCZ696 400mg) +/- Amlodipine

Reporting group description:

Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target

Reporting group title	Olmesartan 40mg +/- Amlodipine

Reporting group description:

Optional amlodipine 2.5 to 10 mg add-on after Week 12 to reach blood pressure target

Serious adverse events	Initiation dose : sacubitril/valsartan (LCZ696 200mg)	Initiation dose: olmesartan 20mg	Maintenance Dose: sacubitril/valsartan (LCZ696 400mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	0 / 57 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			

subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertensive crisis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fat necrosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodule			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Maintenance Dose: olmesartan 40 mg	Sacubitril/valsartan (LCZ696 400mg) +/- Amlodipine	Olmesartan 40mg +/- Amlodipine
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 56 (3.57%)	6 / 54 (11.11%)	5 / 53 (9.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			

subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fat necrosis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodule			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Initiation dose : sacubitril/valsartan (LCZ696 200mg)	Initiation dose: olmesartan 20mg	Maintenance Dose: sacubitril/valsartan (LCZ696 400mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 57 (5.26%)	6 / 57 (10.53%)	10 / 57 (17.54%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	2 / 57 (3.51%)
occurrences (all)	0	2	3
Dizziness			
subjects affected / exposed	1 / 57 (1.75%)	2 / 57 (3.51%)	4 / 57 (7.02%)
occurrences (all)	1	2	4
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	1 / 57 (1.75%)
occurrences (all)	0	0	1
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 57 (0.00%)	0 / 57 (0.00%)	0 / 57 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	4 / 57 (7.02%)
occurrences (all)	0	2	5

Non-serious adverse events	Maintenance Dose: olmesartan 40 mg	Sacubitril/valsartan (LCZ696 400mg) +/- Amlodipine	Olmesartan 40mg +/- Amlodipine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 56 (25.00%)	16 / 54 (29.63%)	24 / 53 (45.28%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 56 (10.71%)	2 / 54 (3.70%)	2 / 53 (3.77%)
occurrences (all)	6	10	5
Dizziness			
subjects affected / exposed	1 / 56 (1.79%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	4 / 53 (7.55%)
occurrences (all)	0	1	4

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 56 (3.57%)	3 / 54 (5.56%)	0 / 53 (0.00%)
occurrences (all)	2	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	3 / 53 (5.66%)
occurrences (all)	0	1	3
Back pain			
subjects affected / exposed	5 / 56 (8.93%)	1 / 54 (1.85%)	5 / 53 (9.43%)
occurrences (all)	5	2	6
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	3 / 53 (5.66%)
occurrences (all)	0	1	3
Nasopharyngitis			
subjects affected / exposed	5 / 56 (8.93%)	11 / 54 (20.37%)	10 / 53 (18.87%)
occurrences (all)	5	14	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2013	The reason for this protocol amendment was a change in the recommended BP targets for patients with diabetes or chronic kidney disease as laid out in the most recent ESC guidance. The new ESC guidance was issued after the original release date of this study protocol. The second change relates to clarification of the amlodipine dosing regimen. The selection of the starting dose was up to the discretion of the investigator to allow for individualized treatment and utilization of the different approved doses of amlodipine in the different countries. Finally, the background section and benefit-risk assessment were updated to describe the observation in a non-human primate study of an increase in amyloid beta in the cerebrospinal fluid when treated with LCZ696 for 2 weeks. This finding was reported to health authorities, ethics committees and investigators separately.
18 June 2014	The reason for this protocol amendment was to update the protocol with the latest safety information regarding the increase in CSF amyloid beta that was observed in monkeys.A study in humans has concluded that this effect was not reproduced in humans. Another reason for this protocol amendment was to change the timing of assessment of the study's primary and secondary objectives from 12 weeks to 52 weeks (12 months). An interim analysis (IA) was initially planned when approximately 128 evaluable patients completed the 12 week assessments. With the change from 12 to 52 weeks in the timing of the primary and secondary endpoints, the week 12 IA was no longer needed. Hence the 12 week IA was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported