Clinical trial results:
A randomized, 8-week, double-blind, parallel-group, activecontrolled, multi-center study to evaluate the efficacy and safety of LCZ696 200 mg in comparison with olmesartan 20 mg in patients with essential hypertension not adequately responsive to olmesartan 20 mg treatment

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2013-001783-36
Trial protocol	ES
Global end of trial date	14 August 2014

Results information

Result version number	v1 (current)
This version publication date	20 May 2016
First version publication date	20 May 2016

Trial information

Trial identification

Sponsor protocol code	CLCZ696A2318

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	14 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of LCZ696 200 mg compared to olmesartan 20 mg in patients with essential hypertension that do not have a satisfactory response to olmesartan 20 mg by testing the hypothesis of superior reduction in mean 24-hour ambulatory systolic blood pressure (maSBP) after 8 weeks of treatment

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	09 September 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	Argentina: 62
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Guatemala: 21
Country: Number of subjects enrolled	Philippines: 40
Country: Number of subjects enrolled	Russian Federation: 42
Country: Number of subjects enrolled	United States: 172
Worldwide total number of subjects	375
EEA total number of subjects	38

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)	287
From 65 to 84 years	87
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Randomized 376 patients but one was incorrectly randomized to the olmesartan 20 mg treatment but did not receive any double-blind medication, and hence was excluded from analysis sets.

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, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696 200 mg

Arm description:

Patients will be treated with one LCZ696 200 mg tablet and one placebo of olmesartan 20 mg capsule once daily for 8 weeks.

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:

LCZ696 200 mg

Arm title	Olmesartan 20 mg

Arm description:

Patients will be treated with one placebo of LCZ696 200 mg tablet and one olmesartan 20 mg capsule once daily for 8 weeks.

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

Number of subjects in period 1	LCZ696 200 mg	Olmesartan 20 mg
Started	188	187
Full analysis set (FAS)	188	187
Safety set (SAF)	188	187
Completed	179	175
Not completed	9	12
Physician decision	-	2
Adverse event, non-fatal	2	5
Protocol deviation	3	2
Non-compliance	-	1
Lost to follow-up	-	1
Subject/guardian decision	3	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	LCZ696 200 mg
Reporting group description:	
Patients will be treated with one LCZ696 200 mg tablet and one placebo of olmesartan 20 mg capsule once daily for 8 weeks.	
Reporting group title	Olmesartan 20 mg
Reporting group description:	
Patients will be treated with one placebo of LCZ696 200 mg tablet and one olmesartan 20 mg capsule once daily for 8 weeks.	

Reporting group values	LCZ696 200 mg	Olmesartan 20 mg	Total
Number of subjects	188	187	375
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	144	143	287
From 65-84 years	43	44	87
85 years and over	1	0	1
Age Continuous | Units: Years			
arithmetic mean	57.1	58	
standard deviation	± 10.19	± 9.09	-
Gender, Male/Female Units: Participants			
Female	91	92	183
Male	97	95	192

End points

End points reporting groups

Reporting group title	LCZ696 200 mg
Reporting group description:	
Patients will be treated with one LCZ696 200 mg tablet and one placebo of olmesartan 20 mg capsule once daily for 8 weeks.	
Reporting group title	Olmesartan 20 mg
Reporting group description:	
Patients will be treated with one placebo of LCZ696 200 mg tablet and one olmesartan 20 mg capsule once daily for 8 weeks.	

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

End point title	Change from baseline in 24-hour mean ambulatory systolic blood pressure (maSBP)
End point description:	
Twenty-four hour mean ambulatory blood pressure measurements (ABPM) will be performed at baseline and at end of study (week 8). The first 24-hour ABPM will be performed beginning at 24 hours prior to baseline visit and the second will be performed 24 hours prior to week 8 visit.	
End point type	Primary
End point timeframe:	
baseline, 8 weeks	

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	164		
Units: mmHg				
least squares mean (standard error)	-4.26 (± 0.6)	-1.04 (± 0.61)		

Statistical analyses

Statistical analysis title	Change from baseline in 24-hour (maSBP)
Comparison groups	LCZ696 200 mg v Olmesartan 20 mg
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.73
upper limit	-1.65
Variability estimate	Standard error of the mean
Dispersion value	0.78

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

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

End point description:

Twenty-four hour mean ambulatory blood pressure measurements (ABPM) will be performed at baseline and at end of study (week 8). The 24-hour ABPM measurements are performed beginning 24 hours prior to baseline and week 8 visits.

End point type	Secondary

End point timeframe:

baseline, 8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	164		
Units: mmHg				
least squares mean (standard error)	-2.27 (± 0.39)	-0.35 (± 0.39)		

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:

Sitting blood pressure (BP) measurement will be taken at every visit from screening through end of study. For each participant at each visit, four separate sitting BP measurements will be obtained (with a full two minute interval between measurements) and averaged to obtain the mean

End point type	Secondary

End point timeframe:

baseline, 8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: mmHg				
least squares mean (standard error)	-14.21 (± 1.28)	-10.03 (± 1.29)		

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:

Sitting blood pressure (BP) measurement will be taken at every visit from screening through end of study. For each participant at each visit, four separate sitting BP measurements will be obtained (with a full two minute interval between measurements) and averaged to obtain the mean

End point type	Secondary

End point timeframe:

baseline, 8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: mmHg				
least squares mean (standard error)	-7.52 (± 0.7)	-4.47 (± 0.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in office pulse pressure

End point title	Change from baseline in office pulse pressure

End point description:

Mean sitting pulse pressure (msPP) will be calculated at screening through end of study at every visit. Mean sitting pulse pressure is calculated as msSBP-msDBP.

End point type	Secondary

End point timeframe:

baseline, 8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: mmHg				
least squares mean (standard error)	-6.67 (± 0.94)	-5.54 (± 0.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving successful overall blood pressure control

End point title	Number of patients achieving successful overall blood pressure control

End point description:

Successful overall blood pressure control is defined as both msSBP/msDBP <140/90 mmHg

End point type	Secondary

End point timeframe:

8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: Participants	76	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving successful mean sitting systolic blood pressure (msSBP) control

End point title	Number of patients achieving successful mean sitting systolic blood pressure (msSBP) control

End point description:

Successful mean sitting systolic blood pressure control is defined as msSBP <140 mmHg

End point type	Secondary

End point timeframe:

8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: Participants	84	58		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving successful mean sitting diastolic blood pressure (msDBP) control

End point title	Number of patients achieving successful mean sitting diastolic blood pressure (msDBP) control

End point description:

Successful mean sitting diastolic blood pressure control is defined as msDBP <90 mmHg or reduction >=10 mmHg

End point type	Secondary

End point timeframe:

8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: Participants	133	112		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving successful mean sitting systolic blood pressure (msSBP) response

End point title	Number of patients achieving successful mean sitting systolic blood pressure (msSBP) response

End point description:

Successful mean sitting systolic blood pressure response is defined as msSBP <140 mmHg or a reduction ≥ 20 mmHg from baseline.

End point type	Secondary

End point timeframe:

baseline, 8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: Participants	90	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving successful mean sitting diastolic blood pressure (msDBP) response

End point title	Number of patients achieving successful mean sitting diastolic blood pressure (msDBP) response

End point description:

Successful mean sitting diastolic blood pressure response is defined as msDBP <90 mmHg or a reduction ≥10 mmHg from baseline.

End point type	Secondary

End point timeframe:

baseline, 8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: Participants	137	115		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of patients with total adverse events, serious adverse events and death were reported.

End point type	Secondary

End point timeframe:

8 weeks

End point values	LCZ696 200 mg	Olmesartan 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: Number of participants				
Adverse events (serious and non-serious)	44	41		
Serious Adverse Events	0	2		
Deaths	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 reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	LCZ696 200 mg
Reporting group description:	
LCZ696 200 mg	
Reporting group title	OLMESARTAN 20 mg
Reporting group description:	
OLMESARTAN 20 mg	

Serious adverse events	LCZ696 200 mg	OLMESARTAN 20 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 188 (0.00%)	2 / 187 (1.07%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BENIGN NEOPLASM OF THYROID GLAND			
subjects affected / exposed	0 / 188 (0.00%)	1 / 187 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 188 (0.00%)	1 / 187 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	LCZ696 200 mg	OLMESARTAN 20 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 188 (3.72%)	10 / 187 (5.35%)	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	5 / 188 (2.66%)	6 / 187 (3.21%)	
occurrences (all)	5	6	
DIZZINESS			
subjects affected / exposed	2 / 188 (1.06%)	4 / 187 (2.14%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported