



## Clinical trial results:

### A randomized, double-blind, parallel group study to evaluate metabolic effects of LCZ696 and amlodipine in obese hypertensive subjects

#### Summary

EudraCT number	2012-002606-40
Trial protocol	DE NL
Global end of trial date	29 July 2013

#### Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	18 July 2015

#### Trial information

##### Trial identification

Sponsor protocol code	CLCZ696B2207
-----------------------	--------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01631864
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	29 July 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 July 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of LCZ696 400 mg QD as compared to amlodipine 10 mg QD on insulin sensitivity after 8 weeks of treatment in obese hypertensive subjects.

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	23 October 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	Netherlands: 27
Country: Number of subjects enrolled	Germany: 71
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	91
From 65 to 84 years	7
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

After signing the Informed Consent, patients underwent screening assessments. If eligibility criteria were met, patients proceeded to the wash-out period (wash-out from previous anti-hypertensive medication).

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	LCZ696

Arm description:

LCZ696 400 mg + placebo to amlodipine 10 mg (2 x placebo to matching amlodipine 5 mg)

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

Dosage and administration details:

Patients received LCZ696 400 mg tablets for oral administration for 56 days.

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

Dosage and administration details:

Patients received matching placebo 10 mg (2 x placebo to matching amlodipine 5 mg) for 56 days.

<b>Arm title</b>	Amlodipine
------------------	------------

Arm description:

Patients received amlodipine 10 mg for 56 days.

Arm type	Experimental
Investigational medicinal product name	Amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Amlodipine 10 mg provided 5 mg tablets

Investigational medicinal product name	Matching placebo for LCZ696
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to LCZ696 400 mg

<b>Number of subjects in period 1</b>	LCZ696	Amlodipine
Started	50	48
Completed	48	44
Not completed	2	4
Adverse event, non-fatal	2	3
'Subject/guardian decision '	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	LCZ696
-----------------------	--------

Reporting group description:

LCZ696 400 mg + placebo to amlodipine 10 mg (2 x placebo to matching amlodipine 5 mg)

Reporting group title	Amlodipine
-----------------------	------------

Reporting group description:

Patients received amlodipine 10 mg for 56 days.

Reporting group values	LCZ696	Amlodipine	Total
Number of subjects	50	48	98
Age categorical Units: Subjects			
Adults (18-64 years)	47	44	91
From 65-84 years	3	4	7
Age continuous Units: years			
arithmetic mean	51.9	50.5	
standard deviation	± 9.6	± 9.4	-
Gender categorical Units: Subjects			
Female	9	13	22
Male	41	35	76

## End points

### End points reporting groups

Reporting group title	LCZ696
Reporting group description: LCZ696 400 mg + placebo to amlodipine 10 mg (2 x placebo to matching amlodipine 5 mg)	
Reporting group title	Amlodipine
Reporting group description: Patients received amlodipine 10 mg for 56 days.	

### Primary: Change from baseline in insulin sensitivity index (SI) to Day 56

End point title	Change from baseline in insulin sensitivity index (SI) to Day 56
End point description: The insulin sensitivity index was assessed by hyperinsulinemic euglycemic clamp. The insulin sensitivity index was calculated from steady-state glucose infusion rates, and blood insulin and glucose concentrations. The unit of measure is ( $\mu\text{g/kg}\cdot\text{min}/(\text{mmol/L}\cdot\text{pmol/L})$ ). The pharmacodynamic (PD) set was used for the analysis. The PD analysis set included all patients with available PD data and no protocol deviations with relevant impact on PD data.	
End point type	Primary
End point timeframe: Baseline, Day 56	

End point values	LCZ696	Amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48 <sup>[1]</sup>	41 <sup>[2]</sup>		
Units: $\mu\text{g/kg}\cdot\text{min}/(\text{mmol/L}\cdot\text{pmol/L})$				
least squares mean (confidence interval 95%)				
Mean Change from baseline	0.192 (0.025 to 0.359)	0.065 (-0.116 to 0.246)		

Notes:

[1] - PD analysis set- Only patients who had both baseline and Day 56 values are included in the analysis

[2] - PD analysis set- Only patients who had both baseline and Day 56 values are included in the analysis

### Statistical analyses

Statistical analysis title	change from baseline-LCZ696 400mg-Amlodipine 10mg
Statistical analysis description: Comparison of change from baseline in insulin sensitivity index (SI) between treatments. Data were analyzed using an ANCOVA with treatment as fixed effect and baseline as covariate	
Comparison groups	LCZ696 v Amlodipine

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	ANCOVA
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.119
upper limit	0.374

### Secondary: Subcutaneous adipose tissue lipolysis - Glycerol (free)

End point title	Subcutaneous adipose tissue lipolysis - Glycerol (free)
End point description: Lipolysis was assessed through subcutaneous adipose tissue microdialysis in the fasted state before (Day 1) and at the end of the eight week treatment period (Day 57). Lipolysis was assessed during a 30 min and 45 min interval at rest. Pharmacodynamic set was included analysis.	
End point type	Secondary
End point timeframe: After 8 weeks of treatment (Day 57)	

End point values	LCZ696	Amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	42		
Units: µmol/L				
geometric mean (confidence interval 95%)				
30 minutes	83.74 (75.35 to 94.61)	67.89 (60.18 to 76.59)		
45 minutes	80.53 (72.81 to 89.06)	63.99 (57.52 to 71.2)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: oxidative metabolism as assessed by indirect calorimetry

End point title	oxidative metabolism as assessed by indirect calorimetry
End point description: Oxidative metabolism at rest was assessed through measurement of oxygen consumption and carbon dioxide production (indirect calorimetry) at baseline and day 57.	
End point type	Secondary
End point timeframe: Day 57	

End point values	LCZ696	Amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	40		
Units: Carbon Dioxide to Oxygen Ratio				
arithmetic mean (confidence interval 95%)	0.787 (0.76 to 0.814)	0.775 (0.746 to 0.804)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of patients that experienced at least one adverse event (AE)

End point title	Percentage of patients that experienced at least one adverse event (AE)
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

8 weeks

End point values	LCZ696	Amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	48		
Units: percentage of participants				
number (not applicable)	60	77.1		

### 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	16.1

### Reporting groups

Reporting group title	Amlodipine 10mg QD
-----------------------	--------------------

Reporting group description:

Amlodipine 10mg QD

Reporting group title	LCZ696 400mg QD
-----------------------	-----------------

Reporting group description:

LCZ696 400mg QD

Serious adverse events	Amlodipine 10mg QD	LCZ696 400mg QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)	1 / 50 (2.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
RUPTURED CEREBRAL ANEURYSM			
subjects affected / exposed	0 / 48 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	1 / 48 (2.08%)	0 / 50 (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 %

<b>Non-serious adverse events</b>	Amlodipine 10mg QD	LCZ696 400mg QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 48 (64.58%)	24 / 50 (48.00%)	
Vascular disorders			
CIRCULATORY COLLAPSE			
subjects affected / exposed	7 / 48 (14.58%)	2 / 50 (4.00%)	
occurrences (all)	8	2	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 48 (2.08%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
HEADACHE			
subjects affected / exposed	7 / 48 (14.58%)	4 / 50 (8.00%)	
occurrences (all)	9	4	
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	16 / 48 (33.33%)	1 / 50 (2.00%)	
occurrences (all)	16	1	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 48 (2.08%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	0 / 48 (0.00%)	5 / 50 (10.00%)	
occurrences (all)	0	5	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	8 / 48 (16.67%)	9 / 50 (18.00%)	
occurrences (all)	9	9	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2012	Added a clarification to the statistical analysis section as requested by the German ethical committee.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported