Clinical trial results:
A randomized, study in healthy subjects to determine the bioavailability of 200 mg LCZ696 mini-tablet compared to the 200 mg LCZ696 final market image tablet

Summary

EudraCT number	2017-001803-57
Trial protocol	Outside EU/EEA
Global end of trial date	05 July 2014

Results information

Result version number	v1 (current)
This version publication date	22 December 2017
First version publication date	22 December 2017

Trial information

Trial identification

Sponsor protocol code	CLCZ696B2126

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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000316-PIP02-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 July 2014
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

To investigate the relative bioavailability of the LCZ696 200 mg mini-tablets compared to the LCZ696 200 mg final market image (FMI) tablet after single administration in healthy subjects under fasted condition.
To evaluate the effect of a small amount of soft food (vanilla pudding) on the bioavailability of a single oral dose of LCZ696 200 mg mini-tablets in healthy subjects under fasted condition.
To evaluate the effect of a high fat meal on the bioavailability of a single oral dose of LCZ696 200 mg mini-tablets sprinkled on vanilla pudding in healthy 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	24 May 2014
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	United States: 40
Worldwide total number of subjects	40
EEA total number of subjects	0

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)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was an open-labeled, randomized, four-sequence, four-period, crossover study in healthy subjects. The study consisted of a maximum 21-day Screening period and four treatment periods.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Sequence 1

Arm description:

Sequence 1: A/B/C/D;
Treatment A: LCZ696 200 mg FMI tablet
Treatment B: LCZ696 200 mg mini-tablets
Treatment C: LCZ696 200 mg mini-tablets with pudding
Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal

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

Dosage and administration details:

Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.

Investigational medicinal product name	LCZ696 200 mg mini-tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.

Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study medication (mini-tablets) sprinkled on a tablespoon of vanilla pudding was administered by the study center personnel in the morning followed by 240 mL of water under fasted condition.

Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding/high fat meal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered LCZ696 200 mg mini-tablets sprinkled on a tablespoon of vanilla pudding 30 minutes after the start of high fat breakfast (800-1000 kcal; ~15% protein, ~25% carbohydrate and ~60% fat), followed by 240 mL of water.

Arm title	Sequence 2

Arm description:

Sequence 2: B/D/A/C;
Treatment A: LCZ696 200 mg FMI tablet
Treatment B: LCZ696 200 mg mini-tablets
Treatment C: LCZ696 200 mg mini-tablets with pudding
Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal

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

Dosage and administration details:

Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.

Investigational medicinal product name	LCZ696 200 mg mini-tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.

Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study medication (mini-tablets) sprinkled on a tablespoon of vanilla pudding was administered by the study center personnel in the morning followed by 240 mL of water under fasted condition.

Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding/high fat meal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered LCZ696 200 mg mini-tablets sprinkled on a tablespoon of vanilla pudding 30 minutes after the start of high fat breakfast (800-1000 kcal; ~15% protein, ~25% carbohydrate and ~60% fat), followed by 240 mL of water.

Arm title	Sequence 3

Arm description:

Sequence 3: C/A/D/B;
Treatment A: LCZ696 200 mg FMI tablet
Treatment B: LCZ696 200 mg mini-tablets
Treatment C: LCZ696 200 mg mini-tablets with pudding
Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal

Arm type	Experimental

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

Dosage and administration details:

Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.

Investigational medicinal product name	LCZ696 200 mg mini-tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.

Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study medication (mini-tablets) sprinkled on a tablespoon of vanilla pudding was administered by the study center personnel in the morning followed by 240 mL of water under fasted condition.

Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding/high fat meal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered LCZ696 200 mg mini-tablets sprinkled on a tablespoon of vanilla pudding 30 minutes after the start of high fat breakfast (800-1000 kcal; ~15% protein, ~25% carbohydrate and ~60% fat), followed by 240 mL of water.

Arm title	Sequence 4

Arm description:

Sequence 4: D/C/B/A;
Treatment A: LCZ696 200 mg FMI tablet
Treatment B: LCZ696 200 mg mini-tablets
Treatment C: LCZ696 200 mg mini-tablets with pudding
Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal

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

Dosage and administration details:

Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.

Investigational medicinal product name	LCZ696 200 mg mini-tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:	
Study medication was administered by the study center personnel with 240 mL of water in the morning following an overnight fast of at least 10 h.	
Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Study medication (mini-tablets) sprinkled on a tablespoon of vanilla pudding was administered by the study center personnel in the morning followed by 240 mL of water under fasted condition.	
Investigational medicinal product name	LCZ696 200 mg mini-tablets/pudding/high fat meal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects were orally administered LCZ696 200 mg mini-tablets sprinkled on a tablespoon of vanilla pudding 30 minutes after the start of high fat breakfast (800-1000 kcal; ~15% protein, ~25% carbohydrate and ~60% fat), followed by 240 mL of water.	

Number of subjects in period 1	Sequence 1	Sequence 2	Sequence 3
Started	10	10	10
Completed	9	10	10
Not completed	1	0	0
Protocol deviation	1	-	-

Number of subjects in period 1	Sequence 4
Started	10
Completed	10
Not completed	0
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	42.0		
standard deviation	± 8.48	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	30	30	

End points

End points reporting groups

Reporting group title	Sequence 1
Reporting group description:	
Sequence 1: A/B/C/D; Treatment A: LCZ696 200 mg FMI tablet Treatment B: LCZ696 200 mg mini-tablets Treatment C: LCZ696 200 mg mini-tablets with pudding Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal	
Reporting group title	Sequence 2
Reporting group description:	
Sequence 2: B/D/A/C; Treatment A: LCZ696 200 mg FMI tablet Treatment B: LCZ696 200 mg mini-tablets Treatment C: LCZ696 200 mg mini-tablets with pudding Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal	
Reporting group title	Sequence 3
Reporting group description:	
Sequence 3: C/A/D/B; Treatment A: LCZ696 200 mg FMI tablet Treatment B: LCZ696 200 mg mini-tablets Treatment C: LCZ696 200 mg mini-tablets with pudding Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal	
Reporting group title	Sequence 4
Reporting group description:	
Sequence 4: D/C/B/A; Treatment A: LCZ696 200 mg FMI tablet Treatment B: LCZ696 200 mg mini-tablets Treatment C: LCZ696 200 mg mini-tablets with pudding Treatment D: LCZ696 200 mg mini-tablets with pudding and high fat meal	
Subject analysis set title	LCZ696 200 mg mini-tablets
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The investigational drug, LCZ696 3.125 mg mini-tablets; 200 mg dose was given as 64 mini-tablets.	
Subject analysis set title	LCZ696 200 mg FMI tablet
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The investigational drug, LCZ696 200 mg final market image (FMI) tablet.	
Subject analysis set title	LCZ696 200 mg mini-tablets with pudding
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Study medication sprinkled on a tablespoon of vanilla pudding was administered by the study center personnel in the morning followed by 240 mL of water under fasted condition.	
Subject analysis set title	LCZ696 200 mg mini-tablets with pudding and high fat meal
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects were administered LCZ696 200 mg mini-tablets sprinkled on a tablespoon of vanilla pudding by mouth 30 minutes after the start of high fat breakfast. Study drug was administered with 240 mL of water.	

Primary: Adjusted Geometric mean of AUCinf for comparison of mini-tablets and FMI tablets for LCZ696 – Completers

End point title	Adjusted Geometric mean of AUCinf for comparison of mini-tablets and FMI tablets for LCZ696 – Completers

End point description:

AUCinf measures the area under the plasma concentration-time curve from time zero to infinity [ng*h/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h post-dose.

End point values	LCZ696 200 mg mini-tablets	LCZ696 200 mg FMI tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40[1]	40[2]		
Units: ng*h/mL				
number (not applicable)				
Analyte AHU377	1914	2002		
Analyte LBQ657	79673	81590		
Analyte Valsartan	21414	19251		

Notes:

[1] - PK analysis set n= 40, 40, 37

[2] - PK analysis set n= 40, 40, 37

Statistical analyses

Statistical analysis title	Comparison result - AUCinf AHU377
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1

Statistical analysis title	Comparison result - AUCinf LBQ657
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.98

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	0.99

Statistical analysis title	Comparison result - AUCinf Valsartan
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.24

Primary: Adjusted Geometric mean of AUClast for comparison of mini-tablets and FMI tablets for LCZ696 – Completers

End point title	Adjusted Geometric mean of AUClast for comparison of mini-tablets and FMI tablets for LCZ696 – Completers

End point description:

AUClast measures the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration [ng*h/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h postdose.

End point values	LCZ696 200 mg mini-tablets	LCZ696 200 mg FMI tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40[3]	40[4]		
Units: ng*h/mL				
number (not applicable)				
Analyte AHU377	1910	1997		
Analyte LBQ657	79005	80929		
Analyte Valsartan	20772	18798		

Notes:

[3] - PK analysis set

[4] - PK analysis set

Statistical analyses

Statistical analysis title	Comparison result - AUClast AHU377
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1

Statistical analysis title	Comparison result - AUClast LBQ657
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	0.99

Statistical analysis title	Comparison result - AUClast Valsartan
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.22

Primary: Adjusted Geometric mean of Cmax for comparison of mini-tablets and FMI tablets for LCZ696 – Completers

End point title	Adjusted Geometric mean of Cmax for comparison of mini-

	tablets and FMI tablets for LCZ696 – Completers

End point description:

Cmax measures the observed maximum plasma concentration following drug administration [ng/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h postdose.

End point values	LCZ696 200 mg mini-tablets	LCZ696 200 mg FMI tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40[5]	40[6]		
Units: ng/mL				
number (not applicable)				
Analyte AHU377	1623	1721		
Analyte LBQ657	7374	7771		
Analyte Valsartan	3767	3459		

Notes:

[5] - PK analysis set

[6] - PK analysis set

Statistical analyses

Statistical analysis title	Comparison result - Cmax AHU377
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.94
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	1.11

Statistical analysis title	Comparison result - Cmax LBQ657
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.95

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.91
upper limit	0.99

Statistical analysis title	Comparison result - Cmax Valsartan
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg FMI tablet
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	1.21

Primary: Adjusted Geometric mean of AUCinf for comparison for mini-tablets with pudding and Mini-tablets for LCZ696 – Completers

End point title	Adjusted Geometric mean of AUCinf for comparison for mini-tablets with pudding and Mini-tablets for LCZ696 – Completers

End point description:

AUCinf measures the area under the plasma concentration-time curve from time zero to infinity [ng*h/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h postdose.

End point values	LCZ696 200 mg mini-tablets	LCZ696 200 mg mini-tablets with pudding		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40[7]	40[8]		
Units: ng*h/mL				
number (not applicable)				
Analyte AHU377	1930	2005		
Analyte LBQ657	79831	80421		
Analyte Valsartan	21226	21598		

Notes:

[7] - PK analysis set n= 39, 39, 38

[8] - PK analysis set n= 39, 39, 38

Statistical analyses

Statistical analysis title	Comparison result - AUCinf AHU377
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.08

Statistical analysis title	Comparison result - AUCinf LBQ657
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.99
upper limit	1.03

Statistical analysis title	Comparison result - AUCinf Valsartan
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.11

Primary: Adjusted Geometric mean of AUClast for comparison for mini-tablets with

pudding and Mini-tablets for LCZ696 – Completers	
End point title	Adjusted Geometric mean of AUClast for comparison for mini-tablets with pudding and Mini-tablets for LCZ696 – Completers

End point description:

AUClast measures the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration [ng*h/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h postdose.

End point values	LCZ696 200 mg mini-tablets	LCZ696 200 mg mini-tablets with pudding		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39[9]	39[10]		
Units: ng*h/mL				
number (not applicable)				
Analyte AHU377	1926	2001		
Analyte LBQ657	79175	79731		
Analyte Valsartan	20598	21343		

Notes:

[9] - PK analysis set

[10] - PK analysis set

Statistical analyses

Statistical analysis title	Comparison result - AUClast AHU377
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.08

Statistical analysis title	Comparison result - AUClast LBQ657
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.99
upper limit	1.03

Statistical analysis title	Comparison result - AUClast Valsartan
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	1.14

Primary: Adjusted Geometric mean of Cmax for comparison for mini-tablets with pudding and Mini-tablets for LCZ696 – Completers

End point title	Adjusted Geometric mean of Cmax for comparison for mini-tablets with pudding and Mini-tablets for LCZ696 – Completers

End point description:

Cmax measures the observed maximum plasma concentration following drug administration [ng/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h postdose.

End point values	LCZ696 200 mg mini-tablets	LCZ696 200 mg mini-tablets with pudding		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39[11]	39[12]		
Units: ng/mL				
number (not applicable)				
Analyte AHU377	1629	1627		
Analyte LBQ657	7373	7279		

Analyte Valsartan	3720	3792		

Notes:

[11] - PK analysis set

[12] - PK analysis set

Statistical analyses

Statistical analysis title	Comparison result - Cmax AHU377
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.85
upper limit	1.18

Statistical analysis title	Comparison result - Cmax LBQ657
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.03

Statistical analysis title	Comparison result - Cmax Valsartan
Comparison groups	LCZ696 200 mg mini-tablets v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.02

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.13

Primary: Adjusted Geometric mean of AUCinf for comparison for mini-tablets with pudding and Mini-tablets with pudding and high fat meal for LCZ696 – Completers

End point title	Adjusted Geometric mean of AUCinf for comparison for mini-tablets with pudding and Mini-tablets with pudding and high fat meal for LCZ696 – Completers

End point description:

AUCinf measures the area under the plasma concentration-time curve from time zero to infinity [ng*h/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h postdose.

End point values	LCZ696 200 mg mini-tablets with pudding	LCZ696 200 mg mini-tablets with pudding and high fat meal		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40[13]	40[14]		
Units: ng*h/mL				
number (not applicable)				
Analyte AHU377	1992	2008		
Analyte LBQ657	80425	81983		
Analyte Valsartan	21878	13032		

Notes:

[13] - PK analysis set n= 38, 39, 35

[14] - PK analysis set n= 38, 39, 35

Statistical analyses

Statistical analysis title	Comparison result - AUCinf AHU377
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.01

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.97
upper limit	1.05

Statistical analysis title	Comparison result - AUCinf LBQ657
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.04

Statistical analysis title	Comparison result - AUCinf Valsartan
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.54
upper limit	0.66

Primary: Adjusted Geometric mean of AUClast for comparison for mini-tablets with pudding and Mini-tablets with pudding and high fat meal for LCZ696 – Completers

End point title	Adjusted Geometric mean of AUClast for comparison for mini-tablets with pudding and Mini-tablets with pudding and high fat meal for LCZ696 – Completers

End point description:

AUClast measures the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration [ng*h/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h

postdose.

End point values	LCZ696 200 mg mini-tablets with pudding	LCZ696 200 mg mini-tablets with pudding and high fat meal		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39[15]	39[16]		
Units: ng*h/mL				
number (not applicable)				
Analyte AHU377	2001	2000		
Analyte LBQ657	79734	81332		
Analyte Valsartan	21376	12653		

Notes:

[15] - PK analysis set

[16] - PK analysis set

Statistical analyses

Statistical analysis title	Comparison result - AUClast AHU377
Comparison groups	LCZ696 200 mg mini-tablets with pudding and high fat meal v LCZ696 200 mg mini-tablets with pudding
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.04

Statistical analysis title	Comparison result - AUClast LBQ657
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.04

Statistical analysis title	Comparison result - AUClast Valsartan
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.59
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.54
upper limit	0.65

Primary: Adjusted Geometric mean of Cmax for comparison for mini-tablets with pudding and Mini-tablets with pudding and high fat meal for LCZ696 – Completers

End point title	Adjusted Geometric mean of Cmax for comparison for mini-tablets with pudding and Mini-tablets with pudding and high fat meal for LCZ696 – Completers

End point description:

Cmax measures the observed maximum plasma concentration following drug administration [ng/mL].

End point type	Primary

End point timeframe:

Pre-dose (0 h) until 96 h postdose. Additional outpatient PK blood sampling at 48, 72, and 96 h postdose.

End point values	LCZ696 200 mg mini-tablets with pudding	LCZ696 200 mg mini-tablets with pudding and high fat meal		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39[17]	39[18]		
Units: ng/mL				
number (not applicable)				
Analyte AHU377	1628	650		
Analyte LBQ657	7279	5872		
Analyte Valsartan	3797	1617		

Notes:

[17] - PK analysis set

[18] - PK analysis set

Statistical analyses

Statistical analysis title	Comparison result - Cmax AHU377
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.34
upper limit	0.46

Statistical analysis title	Comparison result - Cmax LBQ657
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	0.85

Statistical analysis title	Comparison result - Cmax Valsartan
Comparison groups	LCZ696 200 mg mini-tablets with pudding v LCZ696 200 mg mini-tablets with pudding and high fat meal
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	0.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.38
upper limit	0.48

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	LCZ696 200 mg FMI tablet

Reporting group description:

LCZ696 200 mg FMI tablet

Reporting group title	Total

Reporting group description:

Total

Reporting group title	LCZ696 200 mg mini-tablets with pudding

Reporting group description:

LCZ696 200 mg mini-tablets with pudding

Serious adverse events	LCZ696 200 mg FMI tablet	Total	LCZ696 200 mg mini-tablets with pudding
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 39 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	LCZ696 200 mg FMI tablet	Total	LCZ696 200 mg mini-tablets with pudding
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	4 / 40 (10.00%)	3 / 39 (7.69%)
Injury, poisoning and procedural complications			
Laceration			

subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	1 / 39 (2.56%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Vessel puncture site pain			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	1 / 39 (2.56%)
occurrences (all)	0	1	1
Vessel puncture site swelling			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	1 / 39 (2.56%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	1 / 39 (2.56%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	0 / 39 (0.00%)
occurrences (all)	1	1	0

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