Clinical trial results:
A multi-center, prospective, randomized, double-blind study to assess the impact of sacubitril/valsartan vs. enalapril on daily physical activity using a wrist worn actigraphy device in adult chronic heart failure patients

Summary

EudraCT number	2016-003085-32
Trial protocol	DE LT SE EE DK LV BE ES FI FR BG NL IS GR CZ GB
Global end of trial date	11 April 2018

Results information

Result version number	v1
This version publication date	27 April 2019
First version publication date	27 April 2019

Trial information

Trial identification

Sponsor protocol code	CLCZ696B3301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02900378
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2018
Global end of trial reached?	Yes
Global end of trial date	11 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were: • To assess changes from baseline (week 0) in exercise capacity assessed by means of the 6-minute walking test (6MWT) at week 12 in sacubitril/valsartan vs. enalapril treated patients. • To assess changes in daily non-sedentary daytime activity between baseline and after 12 weeks of treatment in sacubitril/valsartan vs. enalapril treated 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	20 December 2016
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	Bulgaria: 22
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Czech Republic: 47
Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Estonia: 56
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 134
Country: Number of subjects enrolled	Greece: 30
Country: Number of subjects enrolled	Iceland: 11
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Latvia: 22
Country: Number of subjects enrolled	Lithuania: 30
Country: Number of subjects enrolled	Netherlands: 29
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Spain: 110
Country: Number of subjects enrolled	Sweden: 8

Country: Number of subjects enrolled	United Kingdom: 26
Worldwide total number of subjects	621
EEA total number of subjects	621

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)	248
From 65 to 84 years	356
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 120 centers in 19 countries worldwide (Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Latvia, Lithuania, Netherlands, Norway, Poland, Spain, Sweden and UK).

Pre-assignment

Screening details:

It was planned to recruit 300 patients per treatment arm, i.e. 600 patients in total. A total of 764 patients were screened, of whom 621 patients were randomized (310 in the sacubitril/valsartan group and 311 in the enalapril group).

Period 1

Period 1 title	Randomization (Visit 2)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696 (Sacubitril/Valsartan)

Arm description:

LCZ696 (Sacubitril/Valsartan) or its matching placebo twice a day for 12 weeks. Patients began study treatment (Sacubitril/Valsartan) at a specific dose level according to their pre-study ACEI/ARB dose (1 (24 mg/26 mg LCZ), 2 (49 mg/51 mg LCZ) or 2a (49 mg/51 mg LCZ)) or matching placebo and were up-titrated according to an up-titration scheme.

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daliy: Sacubitril/valsartan 24 mg/26 mg (LCZ696 50 mg), Sacubitril/valsartan 49 mg/51 mg (LCZ696 100 mg) or Sacubitril/valsartan 97 mg/103 mg (LCZ696 200 mg)

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daliy: Placebo to match sacubitril/valsartan 24 mg/26 mg (LCZ696 50 mg), Placebo to match sacubitril/valsartan 49 mg/51 mg (LCZ696 100 mg) or Placebo to match sacubitril/valsartan 97 mg/103 mg (LCZ696 200 mg)

Arm title	Enalapril

Arm description:

Enalapril or its matching placebo twice a day for 12 weeks. Patients began study treatment (Enalapril) at a specific dose level according to their pre-study ACEI/ARB dose (1 (2.5 mg), 2a (5 mg)) or matching placebo and were up-titrated according to an up-titration scheme.

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily: Placebo to match enalapril 2.5 mg, Placebo to match enalapril 5 mg or Placebo to match enalapril 10 mg

Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily: Enalapril 2.5 mg, Enalapril 5 mg or Placebo to match enalapril 10 mg

Number of subjects in period 1	LCZ696 (Sacubitril/Valsartan)	Enalapril
Started	310	311
Completed	287	283
Not completed	23	28
Adverse event, serious fatal	1	4
Non-compliance with Study Drug	1	1
Adverse event, non-fatal	14	11
Protocol Deviation	1	7
Withdrawal by Parent/Guardian	5	3
Lost to follow-up	1	-
Withdrawal of Informed Consent	-	2

Period 2

Period 2 title	Treatment Phase
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	No

Arm title	LCZ696 (Sacubitril/Valsartan)

Arm description:

LCZ696 (Sacubitril/Valsartan) or its matching placebo twice a day for 12 weeks. Patients began study treatment (Sacubitril/Valsartan) at a specific dose level according to their pre-study ACEI/ARB dose (1 (24 mg/26 mg LCZ), 2 (49 mg/51 mg LCZ) or 2a (49 mg/51 mg LCZ)) or matching placebo and were up-titrated according to an up-titration scheme.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daliy: Placebo to match sacubitril/valsartan 24 mg/26 mg (LCZ696 50 mg), Placebo to match sacubitril/valsartan 49 mg/51 mg (LCZ696 100 mg) or Placebo to match sacubitril/valsartan 97 mg/103 mg (LCZ696 200 mg)

Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daliy: Sacubitril/valsartan 24 mg/26 mg (LCZ696 50 mg), Sacubitril/valsartan 49 mg/51 mg (LCZ696 100 mg) or Sacubitril/valsartan 97 mg/103 mg (LCZ696 200 mg)

Arm title	Enalapril

Arm description:

Enalapril or its matching placebo twice a day for 12 weeks. Patients began study treatment (Enalapril) at a specific dose level according to their pre-study ACEI/ARB dose (1 (2.5 mg), 2a (5 mg)) or matching placebo and were up-titrated according to an up-titration scheme.

Arm type	Active comparator
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily: Enalapril 2.5 mg, Enalapril 5 mg or Placebo to match enalapril 10 mg

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily: Placebo to match enalapril 2.5 mg, Placebo to match enalapril 5 mg or Placebo to match enalapril 10 mg

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: All randomized patients (irrespective as to whether or not they were treated) are included in the randomized set and represented in Period 1. All Demographic and other baseline characteristics were done on the safety and full analysis sets which are represented in Period 2.

Number of subjects in period 2	LCZ696 (Sacubitril/Valsartan)	Enalapril
Started	309	310
Full Analysis Set	302 [2]	302 [3]
Completed	309	310

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The full analysis set (FAS) comprised all patients of the safety data set who provided the baseline value and any post-baseline value of at least one primary endpoint (6MWT or daily non-sedentary daytime activity); 302 patients in each treatment group. The number of patients that started/completed correspond to the safety data set (SAF) consisting of all patients who receivedat least one dose of study medication.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The full analysis set (FAS) comprised all patients of the safety data set who provided the baseline value and any post-baseline value of at least one primary endpoint (6MWT or daily non-sedentary daytime activity); 302 patients in each treatment group. The number of patients that started/completed correspond to the safety data set (SAF) consisting of all patients who receivedat least one dose of study medication.

Baseline characteristics

Reporting groups[1]	
Reporting group title	LCZ696 (Sacubitril/Valsartan)

Reporting group description:

LCZ696 (Sacubitril/Valsartan) or its matching placebo twice a day for 12 weeks. Patients began study treatment (Sacubitril/Valsartan) at a specific dose level according to their pre-study ACEI/ARB dose (1 (24 mg/26 mg LCZ), 2 (49 mg/51 mg LCZ) or 2a (49 mg/51 mg LCZ)) or matching placebo and were up-titrated according to an up-titration scheme.

Reporting group title	Enalapril

Reporting group description:

Enalapril or its matching placebo twice a day for 12 weeks. Patients began study treatment (Enalapril) at a specific dose level according to their pre-study ACEI/ARB dose (1 (2.5 mg), 2a (5 mg)) or matching placebo and were up-titrated according to an up-titration scheme.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number of enrolled patients in the trial (621) is the total number of randomized patients (irrespective as to whether or not they were treated). All Demographic and other baseline characteristics were done on the safety and full analysis sets.

Reporting group values	LCZ696 (Sacubitril/Valsartan)	Enalapril	Total
Number of subjects	309	310	619
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)	118	130	248
From 65-84 years	180	174	354
85 years and over	11	6	17
Age Continuous Units: Years			
arithmetic mean	67.16	66.62	
standard deviation	± 11.04	± 10.45	-
Sex: Female, Male Units: Subjects			
Female	71	61	132
Male	238	249	487
Race/Ethnicity, Customized Units: Subjects			
Black or African American	1	0	1
White	298	299	597
Missing	10	11	21

Subject analysis sets

Subject analysis set title	Safety data set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety data set (SAF) consisted of all patients who received at least one dose of study medication. Safety analyses were performed based on the SAF, and according to the treatment received.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised all patients of the safety data set who provided the baseline value and any post-baseline value of at least one primary endpoint (6MWT or daily non-sedentary daytime activity).

Reporting group values	Safety data set (SAF)	Full analysis set (FAS)	
Number of subjects	619	604	
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)	248	242	
From 65-84 years	354	347	
85 years and over	17	15	
Age Continuous Units: Years			
arithmetic mean	66.89	66.81	
standard deviation	± 10.74	± 10.72	
Sex: Female, Male Units: Subjects			
Female	132	128	
Male	487	476	
Race/Ethnicity, Customized Units: Subjects			
Black or African American	1	1	
White	597	582	
Missing	21	21	

End points

End points reporting groups

Reporting group title	LCZ696 (Sacubitril/Valsartan)

Reporting group description:

LCZ696 (Sacubitril/Valsartan) or its matching placebo twice a day for 12 weeks. Patients began study treatment (Sacubitril/Valsartan) at a specific dose level according to their pre-study ACEI/ARB dose (1 (24 mg/26 mg LCZ), 2 (49 mg/51 mg LCZ) or 2a (49 mg/51 mg LCZ)) or matching placebo and were up-titrated according to an up-titration scheme.

Reporting group title	Enalapril

Reporting group description:

Enalapril or its matching placebo twice a day for 12 weeks. Patients began study treatment (Enalapril) at a specific dose level according to their pre-study ACEI/ARB dose (1 (2.5 mg), 2a (5 mg)) or matching placebo and were up-titrated according to an up-titration scheme.

Reporting group title	LCZ696 (Sacubitril/Valsartan)

Reporting group description:

LCZ696 (Sacubitril/Valsartan) or its matching placebo twice a day for 12 weeks. Patients began study treatment (Sacubitril/Valsartan) at a specific dose level according to their pre-study ACEI/ARB dose (1 (24 mg/26 mg LCZ), 2 (49 mg/51 mg LCZ) or 2a (49 mg/51 mg LCZ)) or matching placebo and were up-titrated according to an up-titration scheme.

Reporting group title	Enalapril

Reporting group description:

Enalapril or its matching placebo twice a day for 12 weeks. Patients began study treatment (Enalapril) at a specific dose level according to their pre-study ACEI/ARB dose (1 (2.5 mg), 2a (5 mg)) or matching placebo and were up-titrated according to an up-titration scheme.

Subject analysis set title	Safety data set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety data set (SAF) consisted of all patients who received at least one dose of study medication. Safety analyses were performed based on the SAF, and according to the treatment received.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised all patients of the safety data set who provided the baseline value and any post-baseline value of at least one primary endpoint (6MWT or daily non-sedentary daytime activity).

Primary: Change from Baseline (Week 0) in the Six Minute Walk Test (6MWT) at end of Study (Week 12)

End point title	Change from Baseline (Week 0) in the Six Minute Walk Test (6MWT) at end of Study (Week 12)

End point description:

The impact of LCZ696 (Sacubitril/Valsartan) and Enalapril on functional exercise capacity was measured by the Six Minute Walk Test at 12 weeks. The 6MWT measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is able to self-pace and rest as needed as they traverse back and forth along a marked walkway.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	310		
Units: meters				
arithmetic mean (standard deviation)				
Baseline (FAS)	365.37 (± 108.18)	371.08 (± 104.41)		
Week 12 (FAS)	395.80 (± 113.11)	395.33 (± 105.94)		
Change from BL at Week 12 (FAS)	31.57 (± 67.35)	24.89 (± 51.64)		
Baseline (FAS without AE/SAE)	364.72 (± 106.86)	371.18 (± 105.13)		
Week 12 (FAS without AE/SAE)	399.31 (± 110.54)	396.02 (± 106.39)		
Change from BL at Week 12 (FAS without AE/SAE)	35.75 (± 58.76)	25.87 (± 51.73)		

Statistical analyses

Statistical analysis title	Change from BL at Week 12 (FAS)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	612
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2464 [1]
Method	ANCOVA
Parameter estimate	Differences of least square means
Point estimate	5.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.93
upper limit	15.29
Variability estimate	Standard error of the mean
Dispersion value	4.89

Notes:

[1] - The comparison of treatment groups were out using an analysis of covariance (ANCOVA) model adjusting for treatment and baseline NYHA class (NYHA II vs. III/IV) and the 6MWT baseline value as covariates.

Statistical analysis title	Change from BL at Week 12 (FAS without AE/SAE)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	612
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0503 [2]
Method	ANCOVA
Parameter estimate	Differences of least square means
Point estimate	8.98

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.31
upper limit	19.27
Variability estimate	Standard error of the mean
Dispersion value	4.58

Notes:

[2] - The comparison of treatment groups were out using an analysis of covariance (ANCOVA) model adjusting for treatment and baseline NYHA class (NYHA II vs. III/IV) and the 6MWT baseline value as covariates.

Primary: Change from Baseline (Week 0) in mean daily non-sedentary daytime activity at end of Study (Week 12)

End point title	Change from Baseline (Week 0) in mean daily non-sedentary daytime activity at end of Study (Week 12)

End point description:

Non-sedentary physical activity is defined as >= 178.50 activity counts per minute; the average number of minutes per day spent in non-sedentary physical activity is being calculated over 14 days before randomization (baseline i.e. week -2 to week 0) and the last 14 days of treatment (i.e. week 10 to week 12).

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline (FAS with MI)	510.11 (± 128.08)	506.81 (± 139.60)		
Week 12 (FAS with MI)	479.69 (± 124.23)	487.53 (± 126.84)		
Change from BL at Week 12 (FAS with MI)	-30.42 (± 102.55)	-19.28 (± 104.04)		
Baseline (FAS with LOCF)	512.07 (± 126.37)	505.31 (± 129.74)		
Week 12 (FAS with LOCF)	489.43 (± 127.36)	490.09 (± 127.82)		
Change from BL at Week 12 (FAS with LOCF)	-21.88 (± 68.55)	-15.41 (± 74.45)		
Baseline (FAS without MI/LOCF)	512.07 (± 126.37)	505.31 (± 129.74)		
Week 12 (FAS without MI/LOCF)	479.81 (± 122.45)	486.85 (± 128.70)		
Change from BL at Week 12 (FAS without MI/LOCF)	-25.14 (± 69.11)	-20.51 (± 72.52)		

Statistical analyses

Statistical analysis title	Change from BL at Week 12 (FAS with MI)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4769 [3]
Method	ANCOVA
Parameter estimate	Differences of least square means
Point estimate	-6.14
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-25.7
upper limit	13.41
Variability estimate	Standard error of the mean
Dispersion value	8.61

Notes:

[3] - The comparison of treatment groups were carried out using an ANCOVA model adjusting for treatment, baseline NYHA class (NYHA II vs. III/IV) and the daily non-sedentary daytime activity baseline value as covariates.

Statistical analysis title	Change from BL at Week 12 (FAS without MI/LOCF)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3513 [4]
Method	ANCOVA
Parameter estimate	Differences of least square means
Point estimate	-6.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.39
upper limit	6.91
Variability estimate	Standard error of the mean
Dispersion value	6.69

Notes:

[4] - The comparison of treatment groups were carried out using an ANCOVA model adjusting for treatment, baseline NYHA class (NYHA II vs. III/IV) and the daily non-sedentary daytime activity baseline value as covariates.

Statistical analysis title	Change from BL at Week 12 (FAS with LOCF)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3463 [5]
Method	ANCOVA
Parameter estimate	Differences of least square means
Point estimate	-5.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.48
upper limit	6.14
Variability estimate	Standard error of the mean
Dispersion value	6.01

Notes:

[5] - The comparison of treatment groups were carried out using an ANCOVA model adjusting for treatment, baseline NYHA class (NYHA II vs. III/IV) and the daily non-sedentary daytime activity baseline value as covariates.

Secondary: Proportion of patients with improved performance (>= 30 m) in the Six Minute Walk Test (6MWT) - FAS

End point title	Proportion of patients with improved performance (>= 30 m) in the Six Minute Walk Test (6MWT) - FAS

End point description:

The proportion of patients with improved performance (>= 30 meters) in the six-minute walk test (6MWT) was assessed by treatment group.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: Participants				
number (not applicable)				
No	142	153		
Yes	149	129		
Missing	11	20		

Statistical analyses

Statistical analysis title	FAS population
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.228
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.882
upper limit	1.708

Secondary: Proportion of patients with improved performance (>= 30 m) in the Six Minute Walk Test (6MWT) - FAS subset without AE/SAE

End point title	Proportion of patients with improved performance (>= 30 m) in the Six Minute Walk Test (6MWT) - FAS subset without AE/SAE

End point description:

The proportion of patients with improved performance (>= 30 meters) in the six-minute walk test (6MWT) was assessed by treatment group.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	294		
Units: Participants				
number (not applicable)				
No	133	146		
Yes	149	129		
Missing	8	19		

Statistical analyses

Statistical analysis title	FAS subset without AE/SAE
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	584
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.251
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.895
upper limit	1.748

Secondary: Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked equal to or less than 300 meters at Baseline - FAS

End point title	Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked equal to or less than 300 meters at Baseline - FAS

End point description:

The proportion of patients with improved performance (>= 30 meters) in the six-minute walk test (6MWT) was assessed by treatment group in a subset of patients with baseline six-minute walk distance equal to or less than 300 meters.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	65		
Units: Participants				
number (not applicable)				
No	35	31		
Yes	41	29		
Missing	2	5		

Statistical analyses

Statistical analysis title	FAS population
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.634
upper limit	2.464

Secondary: Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked equal to or less than 300 meters at Baseline - FAS subset without AE/SAE

End point title	Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked equal to or less than 300 meters at Baseline - FAS subset without AE/SAE

End point description:

The proportion of patients with improved performance (>= 30 meters) in the six-minute walk test (6MWT) was assessed by treatment group in a subset of patients with baseline six-minute walk distance equal to or less than 300 meters.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	63		
Units: Participants				
number (not applicable)				
No	33	30		
Yes	41	29		
Missing	1	4		

Statistical analyses

Statistical analysis title	FAS subset without AE/SAE
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.644
upper limit	2.544

Secondary: Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked 100-450 meters at Baseline - FAS

End point title	Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked 100-450 meters at Baseline - FAS

End point description:

The proportion of patients with improved performance (>= 30 meters) in the six-minute walk test (6MWT) was assessed by treatment group in a subset of patients with baseline six-minute walk distance from 100 to 450 meters.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	238		
Units: Participants				
number (not applicable)				
No	109	121		
Yes	122	105		
Missing	7	12		

Statistical analyses

Statistical analysis title	FAS population
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.863
upper limit	1.811

Secondary: Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked 100-450 meters at Baseline - FAS subset without AE/SAE

End point title	Proportion of patients with improved performance (>= 30 m) in the 6MWT which walked 100-450 meters at Baseline - FAS subset without AE/SAE

End point description:

The proportion of patients with improved performance (>= 30 meters) in the six-minute walk test (6MWT) was assessed by treatment group in a subset of patients with baseline six-minute walk distance from 100 to 450 meters.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	230		
Units: Participants				
number (not applicable)				

No	103	115		
Yes	122	105		
Missing	5	11		

Statistical analyses

Statistical analysis title	FAS subset without AE/SAE
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.865
upper limit	1.834

Secondary: Change from Baseline (Week 0) in the Six Minute Walk Test (6MWT) at Weeks 4 and 8

End point title	Change from Baseline (Week 0) in the Six Minute Walk Test (6MWT) at Weeks 4 and 8

End point description:

The impact of LCZ696 (Sacubitril/Valsartan) and Enalapril on functional exercise capacity was measured by the Six Minute Walk Test at Weeks 4 and 8. The 6MWT measures the distance an individual is able to walf over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is able to self-pace and rest as needed as they traverse back and forth along a marked walkway.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: meters				
arithmetic mean (standard deviation)				
Baseline (FAS)	365.37 (± 108.18)	371.08 (± 104.41)		
Week 4 (FAS)	385.22 (± 110.55)	385.02 (± 109.92)		
Change from BL at Week 4 (FAS)	19.13 (± 49.16)	13.72 (± 51.39)		

Week 8 (FAS)	395.28 (± 112.05)	391.72 (± 108.99)		
Change from BL at Week 8 (FAS)	28.72 (± 57.99)	21.15 (± 52.75)		
Baseline (FAS without AE/SAE)	364.72 (± 106.86)	371.18 (± 105.13)		
Week 4 (FAS without AE/SAE)	384.58 (± 107.69)	385.92 (± 110.81)		
Change from BL at Week 4 (FAS without AE/SAE)	18.91 (± 49.63)	14.45 (± 51.48)		
Week 8 (FAS without AE/SAE)	396.64 (± 110.65)	391.82 (± 109.72)		
Change from BL at Week 8 (FAS without AE/SAE)	30.38 (± 57.07)	21.51 (± 52.99)		

Statistical analyses

Statistical analysis title	Change from BL at Week 4 (FAS)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1814
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4 (FAS without AE/SAE)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3315
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8 (FAS)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2414
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8 (FAS without AE/SAE)
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1793
Method	Wilcoxon (Mann-Whitney)

Secondary: Proportion of patients who show increased levels (>= 10% increase) of non sedentary daytime physical activity at Week 12 compared to Baseline

End point title	Proportion of patients who show increased levels (>= 10% increase) of non sedentary daytime physical activity at Week 12 compared to Baseline

End point description:

Non sedentary physical activity is defined as >= 178.50 activity counts per minute; the everage number of minutes per day spent in non sedentary physical activity will be calculated over 14 days before randomization (baseline) and the last 14 days of treatment (i.e week 10 to week 12)

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: Participants				
number (not applicable)				
No	175	163		
Yes	28	31		
Missing	99	108		

Statistical analyses

Statistical analysis title	>=10% increase level at week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.821
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.462
upper limit	1.457

Secondary: Proportion of patients achieving PGA Score at Weeks 4, 8 and 12

End point title	Proportion of patients achieving PGA Score at Weeks 4, 8 and 12

End point description:

The Patient Global Assessment (PGA) is a self-reported tool to assess the patients' subjective rating of their disease activity widely used in HF research. The patients are asked to report functioning or response to an intervention by rating their current condition compared to their pre-intervention condition on a numerical scale: 1) much improved 2) moderately improved 3) a little improved 4) unchanged 5) a little worse 6) moderately worse or 7) much worse.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: Participants				
number (not applicable)				
Week 4|Has much improved	19	16		
Week 8|Has much improved	23	24		
Week 12|Has much improved	35	40		
Week 4|Has (moderately) improved	63	51		
Week 8|Has (moderately) improved	79	73		
Week 12|Has (moderately) improved	72	67		
Week 4|Has a little improved	94	64		
Week 8|Has a little improved	88	82		
Week 12|Has a little improved	82	74		
Week 4|Is unchanged	98	131		
Week 8|Is unchanged	82	88		
Week 12|Is unchanged	79	94		
Week 4|Is a little worse	13	15		
Week 8|Is a little worse	14	11		
Week 12|Is a little worse	12	7		
Week 4|Is (moderately) worse	3	5		
Week 8|Is (moderately) worse	14	11		
Week 12|Is (moderately) worse	5	3		
Week 4|Is much worse	1	1		
Week 8|Is much worse	0	1		
Week 12|Is much worse	2	2		
Week 4|Missing	11	19		
Week 8|Missing	14	20		
Week 12|Missing	15	15		

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0515
Method	Chi-squared

Statistical analysis title	Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9025
Method	Chi-squared

Statistical analysis title	Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6713
Method	Chi-squared

Secondary: Proportion of patients with improved symptoms of Heart Failure as assessed by Patient Global Assessment (PGA)

End point title	Proportion of patients with improved symptoms of Heart Failure as assessed by Patient Global Assessment (PGA)

End point description:

The Patient Global Assessment (PGA) is a self-reported tool to assess the patients' subjective rating of their disease activity widely used in HF research. The patients are asked to report functioning or response to an intervention by rating their current condition compared to their pre-intervention condition on a numerical scale: 1) much improved 2) moderately improved 3) a little improved 4) unchanged 5) a little worse 6) moderately worse or 7) much worse. Patients with improved symptoms were categorized as: Improvement, Is unchanged, Gets worse or Missing.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: Participants				
number (not applicable)				
Week 4|Improvement	176	131		
Week 8|Improvement	190	179		
Week 12|Improvement	189	181		
Week 4|Is unchanged	98	131		
Week 8|Is unchanged	82	88		
Week 12|Is unchanged	79	94		
Week 4|Gets worse	17	21		
Week 8|Gets worse	16	15		
Week 12|Gets worse	19	12		
Week 4|Missing	11	19		
Week 8|Missing	14	20		
Week 12|Missing	15	15		

Statistical analyses

Statistical analysis title	Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0029
Method	Chi-squared

Statistical analysis title	Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7754
Method	Chi-squared

Statistical analysis title	Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2172
Method	Chi-squared

Secondary: Change from Baseline in mean daily non-sedentary daytime activity in weekly intervals

End point title	Change from Baseline in mean daily non-sedentary daytime activity in weekly intervals

End point description:

Non-sedentary physical activity is defined as >= 178.50 activity counts per minute; Mean daily non-sedentary daytime physical activity were being calculated over weekly and compared to before the inclusion

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11 and Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline	512.07 (± 126.37)	505.31 (± 129.74)		
Week 1	527.34 (± 129.54)	509.28 (± 131.75)		
Change from BL at Week 1	22.60 (± 62.33)	9.88 (± 50.17)		
Week 2	351.19 (± 133.89)	508.70 (± 133.69)		
Change from BL at Week 2	22.80 (± 70.25)	6.19 (± 55.14)		
Week 3	525.98 (± 126.66)	513.63 (± 130.58)		
Change from BL at Week 3	13.55 (± 66.74)	6.40 (± 62.63)		
Week 4	519.43 (± 133.21)	503.25 (± 139.48)		
Change from BL at Week 4	11.99 (± 60.10)	-5.35 (± 72.35)		
Week 5	507.46 (± 129.31)	501.70 (± 138.12)		
Change from BL at Week 5	1.77 (± 71.74)	-10.95 (± 81.39)		
Week 6	504.15 (± 131.05)	500.39 (± 136.08)		
Change from BL at Week 6	-0.44 (± 76.32)	-7.91 (± 69.71)		

Week 7	495.06 (± 127.80)	503.46 (± 136.69)		
Change from BL at Week 7	-10.35 (± 76.94)	-6.54 (± 75.77)		
Week 8	497.62 (± 130.56)	496.45 (± 139.12)		
Change from BL at Week 8	-9.49 (± 79.10)	-9.21 (± 75.23)		
Week 9	496.74 (± 128.90)	497.24 (± 131.02)		
Change from BL at Week 9	-10.09 (± 69.93)	-10.75 (± 75.82)		
Week 10	495.53 (± 130.97)	500.88 (± 138.35)		
Change from BL at Week 10	-9.46 (± 80.47)	-7.52 (± 77.12)		
Week 11	492.28 (± 127.19)	495.14 (± 135.54)		
Change from BL at Week 11	-12.93 (± 74.12)	-11.64 (± 75.35)		
Week 12	492.28 (± 127.19)	495.14 (± 135.54)		
Change from BL at Week 12	-12.93 (± 74.12)	-11.64 (± 75.35)		

Statistical analyses

Statistical analysis title	Change from BL at Week 1
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0008
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0008
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 3
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0297
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0069
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 5
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2275
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3486
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 9
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5301
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7184
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 7
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.68
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 10
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6019
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 11
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8229
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8229
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from Baseline in mean daily non-sedentary daytime activity in two-weekly intervals

End point title	Change from Baseline in mean daily non-sedentary daytime activity in two-weekly intervals

End point description:

Non-sedentary physical activity is defined as >= 178.50 activity counts per minute; Mean daily non-sedentary daytime physical activity were being calculated over two-weekly intervals and compared to before the inclusion

End point type	Secondary

End point timeframe:

Baseline, Weeks 0 to 2, Weeks 2 to 4, Weeks 4 to 6, Weeks 6 to 8, Weeks 8 to 10, Weeks 10 to 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline	512.07 (± 126.37)	505.31 (± 129.74)		
Weeks 0 to 2	529.63 (± 129.31)	509.02 (± 129.97)		
Change from BL at Week 2	22.88 (± 60.90)	8.06 (± 45.65)		
Weeks 2 to 4	522.30 (± 126.68)	508.57 (± 131.41)		
Change from BL at Week 4	12.04 (± 54.84)	0.55 (± 60.23)		
Weeks 4 to 6	505.54 (± 127.40)	500.49 (± 135.70)		
Change from BL at Week 6	0.21 (± 68.47)	-10.86 (± 72.76)		
Weeks 6 to 8	495.94 (± 124.78)	500.92 (± 135.26)		
Change from BL at Week 8	-10.11 (± 71.75)	-7.62 (± 69.96)		
Weeks 8 to 10	496.57 (± 126.68)	497.02 (± 132.96)		
Change from BL at Week 10	-8.44 (± 68.35)	-8.75 (± 71.50)		
Weeks 10 to 12	483.20 (± 121.43)	493.41 (± 130.00)		
Change from BL at Week 12	-21.17 (± 68.77)	-13.93 (± 72.65)		

Statistical analyses

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0123
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.256
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5865
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 10
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5463
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3212
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from Baseline in mean daily Light non-sedentary daytime physical activity

End point title	Change from Baseline in mean daily Light non-sedentary daytime physical activity

End point description:

The average number of minutes per day spent in light non-sedentary physical activity was being calculated over 14 day epochs. Non-sedentary physical activity is defined as >= 178.5 activity counts per minute and light physical activity is defined as 178.5 – 565.5 counts per minute.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11 and Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline	251.94 (± 50.54)	247.30 (± 58.70)		
Week 1	263.17 (± 55.85)	251.37 (± 58.13)		
Change from BL at Week 1	14.10 (± 31.15)	6.28 (± 27.98)		
Week 2	262.42 (± 55.12)	248.33 (± 57.81)		
Change from BL at Week 2	10.91 (± 36.10)	1.58 (± 28.80)		
Week 3	261.80 (± 52.68)	251.12 (± 57.48)		
Change from BL at Week 3	9.68 (± 33.10)	3.61 (± 31.85)		
Week 4	256.10 (± 52.61)	246.97 (± 58.06)		
Change from BL at Week 4	5.14 (± 31.12)	-1.77 (± 33.49)		
Week 5	253.98 (± 54.75)	243.71 (± 59.17)		

Change from BL at Week 5	2.71 (± 37.90)	-5.77 (± 37.14)		
Week 6	252.10 (± 56.73)	244.25 (± 57.33)		
Change from BL at Week 6	1.08 (± 38.80)	-4.72 (± 36.44)		
Week 7	251.02 (± 52.09)	244.85 (± 57.32)		
Change from BL at Week 7	-0.88 (± 38.88)	-3.18 (± 37.27)		
Week 8	251.46 (± 52.21)	245.02 (± 59.31)		
Change from BL at Week 8	-1.71 (± 38.69)	-2.41 (± 36.53)		
Week 9	250.04 (± 52.64)	245.84 (± 56.31)		
Change from BL at Week 9	-2.54 (± 35.74)	-4.52 (± 37.14)		
Week 10	248.33 (± 54.44)	245.62 (± 58.69)		
Change from BL at Week 10	-3.43 (± 42.11)	-2.65 (± 36.76)		
Week 11	248.19 (± 53.09)	244.83 (± 59.77)		
Change from BL at Week 11	-3.86 (± 39.67)	-3.13 (± 34.23)		
Week 12	239.30 (± 52.76)	243.63 (± 56.92)		
Change from BL at Week 12	-11.98 (± 42.07)	-6.55 (± 35.79)		

Statistical analyses

Statistical analysis title	Change from BL at Week 1
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0004
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0009
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 3
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0094
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0301
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 5
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1557
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6461
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3941
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 7
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9759
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 9
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7209
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 11
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7247
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 10
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4444
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2933
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from Baseline in mean daily Moderate-to-Vigorous non-sedentary daytime physical activity

End point title	Change from Baseline in mean daily Moderate-to-Vigorous non-sedentary daytime physical activity

End point description:

The average number of minutes per day spent in moderate to vigorous non-sedentary physical activity was being calculated over 14 day epochs. Non-sedentary physical activity is defined as >= 178.5 activity counts per minute and moderate-to-vigorous activity is defined as > 565.5 counts per minute.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11 and Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline	260.13 (± 110.94)	258.01 (± 111.73)		
Week 1	264.16 (± 109.31)	257.92 (± 111.47)		
Change from BL at Week 1	8.50 (± 45.86)	3.60 (± 39.79)		
Week 2	268.77 (± 114.83)	260.37 (± 116.00)		
Change from BL at Week 2	11.89 (± 50.98)	4.61 (± 45.53)		
Week 3	264.19 (± 108.10)	262.51 (± 111.15)		
Change from BL at Week 3	3.87 (± 49.53)	2.80 (± 51.23)		
Week 4	263.35 (± 114.86)	256.28 (± 115.82)		
Change from BL at Week 4	6.85 (± 43.45)	-3.58 (± 56.76)		
Week 5	253.48 (± 108.52)	257.99 (± 115.65)		
Change from BL at Week 5	-0.93 (± 51.57)	-5.18 (± 66.01)		
Week 6	252.05 (± 108.75)	256.14 (± 115.35)		
Change from BL at Week 6	-1.52 (± 55.23)	-3.19 (± 54.72)		
Week 7	244.04 (± 105.32)	258.61 (± 118.51)		

Change from BL at Week 7	-9.47 (± 57.67)	-3.35 (± 56.28)		
Week 8	246.16 (± 109.03)	251.42 (± 113.84)		
Change from BL at Week 8	-7.78 (± 57.13)	-6.80 (± 57.90)		
Week 9	246.70 (± 106.78)	251.40 (± 108.51)		
Change from BL at Week 9	-7.55 (± 54.98)	-6.23 (± 57.68)		
Week 10	247.20 (± 107.41)	255.26 (± 116.88)		
Change from BL at Week 10	-6.03 (± 57.08)	-4.86 (± 59.50)		
Week 11	244.09 (± 104.33)	250.31 (± 113.81)		
Change from BL at Week 11	-9.57 (± 51.95)	-8.51 (± 61.45)		
Week 12	237.15 (± 100.32)	248.08 (± 113.51)		
Change from BL at Week 12	-20.52 (± 58.37)	-11.57 (± 64.90)		

Statistical analyses

Statistical analysis title	Change from BL at Week 1
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0854
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0528
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 3
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4137
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0082
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 5
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7908
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6499
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 7
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5547
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6961
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 9
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5946
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 10
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8957
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 11
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8468
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1711
Method	Wilcoxon (Mann-Whitney)

Secondary: Total weekly time spent in non-sedentary daytime physical activity

End point title	Total weekly time spent in non-sedentary daytime physical activity

End point description:

Non-sedentary physical activity is defined as >= 178.5 activity counts per minute; The total time spent in non-sedentary physical activity was being calculated for each patient in weekly intervals and the temporal course for each patient was assessed.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11 and Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline	3616.87 (± 964.92)	3528.56 (± 993.10)		
Week 1	3676.46 (± 923.85)	3560.10 (± 916.16)		
Change from BL at Week 1	103.29 (± 509.20)	82.48 (± 588.19)		
Week 2	3691.24 (± 953.03)	3557.71 (± 940.60)		
Change from BL at Week 2	76.23 (± 563.79)	52.38 (± 600.08)		
Week 3	3668.25 (± 894.91)	3580.54 (± 922.70)		
Change from BL at Week 3	25.28 (± 571.36)	34.56 (± 663.68)		
Week 4	3608.39 (± 936.87)	3482.15 (± 991.15)		
Change from BL at Week 4	5.10 (± 497.55)	-56.23 (± 748.35)		
Week 5	3488.43 (± 944.87)	3458.65 (± 973.75)		
Change from BL at Week 5	-116.74 (± 607.31)	-79.18 (± 817.71)		
Week 6	3519.12 (± 922.58)	3489.15 (± 962.55)		
Change from BL at Week 6	-72.08 (± 569.61)	-21.73 (± 724.96)		
Week 7	3444.52 (± 892.15)	3502.67 (± 977.43)		
Change from BL at Week 7	-143.38 (± 605.25)	-36.18 (± 709.43)		
Week 8	3466.82 (± 936.51)	3457.74 (± 993.56)		
Change from BL at Week 8	-130.59 (± 631.30)	-59.92 (± 716.74)		

Week 9	3470.69 (± 913.06)	3447.28 (± 932.67)		
Change from BL at Week 9	-131.08 (± 549.54)	-108.48 (± 719.58)		
Week 10	3444.77 (± 947.18)	3489.68 (± 964.08)		
Change from BL at Week 10	-119.41 (± 648.17)	-68.93 (± 711.22)		
Week 11	3406.56 (± 910.84)	3436.96 (± 971.78)		
Change from BL at Week 11	-170.14 (± 632.53)	-120.35 (± 707.11)		
Week 12	3093.96 (± 913.14)	3234.90 (± 991.50)		
Change from BL at Week 12	-506.82 (± 792.71)	-339.15 (± 786.06)		

Statistical analyses

Statistical analysis title	Change from BL at Week 1
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0065
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0316
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 3
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1342
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4

Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0252
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 5
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9024
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9052
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3174
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 7
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.287
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 9
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.502
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 11
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4823
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 10
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4037
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.109
Method	Wilcoxon (Mann-Whitney)

Secondary: Total weekly time spent in Light non-sedentary daytime physical activity

End point title	Total weekly time spent in Light non-sedentary daytime physical activity

End point description:

Light non-sedentary daytime physical activity is defined as between 178.5 – 565.5 counts per minute; The time spent in light non-sedentary physical activity was being calculated for each patient in weekly intervals and the temporal course for each patient was assessed.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10,

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline	1773.14 (± 392.22)	1721.50 (± 452.26)		
Week 1	1834.71 (± 400.46)	1757.76 (± 407.14)		
Change from BL at Week 1	81.84 (± 255.91)	53.74 (± 282.22)		
Week 2	1823.86 (± 396.55)	1736.64 (± 407.45)		
Change from BL at Week 2	46.26 (± 301.74)	17.26 (± 280.12)		
Week 3	1826.38 (± 376.72)	1751.95 (± 410.11)		
Change from BL at Week 3	46.05 (± 281.11)	24.88 (± 313.52)		
Week 4	1778.88 (± 372.86)	1707.68 (± 410.73)		
Change from BL at Week 4	9.17 (± 275.92)	-18.74 (± 346.02)		
Week 5	1745.87 (± 406.21)	1683.08 (± 429.50)		
Change from BL at Week 5	-36.66 (± 307.01)	-37.98 (± 369.53)		
Week 6	1759.09 (± 397.67)	1701.89 (± 405.01)		
Change from BL at Week 6	-17.85 (± 290.75)	-16.56 (± 343.51)		
Week 7	1747.03 (± 366.43)	1702.58 (± 399.11)		
Change from BL at Week 7	-32.03 (± 307.16)	-17.71 (± 322.33)		
Week 8	1750.02 (± 377.35)	1705.09 (± 424.99)		
Change from BL at Week 8	-37.50 (± 323.19)	-17.49 (± 318.83)		
Week 9	1746.73 (± 375.07)	1706.26 (± 407.89)		
Change from BL at Week 9	-36.47 (± 289.67)	-43.21 (± 341.30)		
Week 10	1724.72 (± 395.95)	1712.55 (± 412.82)		
Change from BL at Week 10	-46.95 (± 339.81)	-22.01 (± 314.65)		
Week 11	1717.08 (± 386.33)	1697.81 (± 429.44)		
Change from BL at Week 11	-60.08 (± 319.85)	-40.52 (± 313.76)		
Week 12	1559.62 (± 428.02)	1607.33 (± 449.83)		

Change from BL at Week 12	-210.49 (± 390.17)	-144.96 (± 339.29)		

Statistical analyses

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0143
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 1
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0061
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 3
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0708
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 5
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8017
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4

Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.075
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7956
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 7
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3499
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1192
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 9
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5237
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 10
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3902
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 11
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4228
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1571
Method	Wilcoxon (Mann-Whitney)

Secondary: Total weekly time spent in Moderate-to-Vigorous non-sedentary daytime physical activity

End point title	Total weekly time spent in Moderate-to-Vigorous non-sedentary daytime physical activity

End point description:

Moderate-to-vigorous non-sedentary physical activity is defined as > 565.5 counts per minute. The total time spent in moderate-to-vigorous non-sedentary physical activity was being calculated for each patient in weekly intervals and the temporal course for each patient was assessed.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11 and Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				
Baseline	1843.73 (± 830.30)	1807.07 (± 815.89)		
Week 1	1841.76 (± 769.54)	1802.34 (± 775.36)		
Change from BL at Week 1	21.45 (± 373.16)	28.75 (± 404.20)		
Week 2	1867.37 (± 806.56)	1821.07 (± 813.27)		
Change from BL at Week 2	29.97 (± 383.31)	35.13 (± 432.43)		
Week 3	1841.87 (± 755.88)	1828.59 (± 777.65)		
Change from BL at Week 3	-20.77 (± 425.19)	9.68 (± 458.99)		
Week 4	1829.51 (± 801.93)	1774.46 (± 815.93)		
Change from BL at Week 4	-4.07 (± 344.29)	-37.49 (± 506.27)		
Week 5	1742.56 (± 767.53)	1775.57 (± 798.92)		
Change from BL at Week 5	-80.08 (± 423.07)	-41.20 (± 577.49)		
Week 6	1760.03 (± 763.64)	1787.26 (± 810.30)		
Change from BL at Week 6	-54.23 (± 416.05)	-5.17 (± 509.74)		
Week 7	1697.49 (± 732.18)	1800.09 (± 829.37)		
Change from BL at Week 7	-111.35 (± 438.85)	-18.47 (± 505.11)		
Week 8	1716.80 (± 769.31)	1752.65 (± 802.46)		
Change from BL at Week 8	-93.09 (± 429.65)	-42.43 (± 522.80)		
Week 9	1723.96 (± 750.60)	1741.02 (± 757.26)		
Change from BL at Week 9	-94.81 (± 407.63)	-65.27 (± 492.38)		
Week 10	1720.06 (± 760.72)	1777.14 (± 811.27)		
Change from BL at Week 10	-72.46 (± 442.80)	-45.92 (± 514.49)		
Week 11	1689.48 (± 731.77)	1739.15 (± 803.36)		
Change from BL at Week 11	-110.06 (± 432.47)	-79.83 (± 516.05)		
Week 12	1534.35 (± 678.12)	1627.57 (± 778.70)		
Change from BL at Week 12	-296.33 (± 525.81)	-194.19 (± 564.53)		

Statistical analyses

Statistical analysis title	Change from BL at Week 1
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3231
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3519
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 3
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8335
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0465
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 5
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5016
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5941
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4125
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 7
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2019
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 9
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5702
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 11
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5343
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 10
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4752
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0985
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from Baseline in peak six minutes of daytime physical activity

End point title	Change from Baseline in peak six minutes of daytime physical activity

End point description:

The peak 6 min walk (M6min) is a parameter derived by validated algorithms of the software that are used to preprocess actigraphy data. The parameter reflected the peak 6 minutes of day time physical activity. The mean daily 6-minute walking test was being calculated over 14 day intervals.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8 and Week 12

End point values	LCZ696 (Sacubitril/Valsartan)	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	302		
Units: minutes				
arithmetic mean (standard deviation)				

Baseline	189.08 (± 76.75)	182.52 (± 60.09)		
Week 2	193.54 (± 77.30)	184.46 (± 59.49)		
Change from BL at Week 2	6.18 (± 46.72)	3.52 (± 32.16)		
Week 4	191.86 (± 80.21)	181.11 (± 61.75)		
Change from BL at Week 4	5.47 (± 50.93)	-0.23 (± 40.44)		
Week 6	191.21 (± 77.38)	181.11 (± 55.07)		
Change from BL at Week 6	2.69 (± 42.51)	-1.02 (± 38.82)		
Week 8	183.96 (± 70.54)	180.92 (± 57.28)		
Change from BL at Week 8	-2.71 (± 41.43)	-0.22 (± 38.05)		
Week 12	184.42 (± 67.09)	180.44 (± 55.36)		
Change from BL at Week 12	-1.07 (± 49.32)	-2.45 (± 39.15)		

Statistical analyses

Statistical analysis title	Change from BL at Week 2
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4525
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 4
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0445
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 6
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1158
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 8
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3901
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from BL at Week 12
Comparison groups	LCZ696 (Sacubitril/Valsartan) v Enalapril
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7725
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse Events were collected for the maximum duration of participants's treatment exposure plus any follow up period, approximately 4 months.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Enalapril
Reporting group description: Enalapril	
Reporting group title	Sacubitril/valsartan
Reporting group description: Sacubitril/valsartan	

Serious adverse events	Enalapril	Sacubitril/valsartan	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 310 (9.03%)	19 / 309 (6.15%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic bronchial carcinoma			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Intermittent claudication			

subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Renal lithiasis prophylaxis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Coronary bypass thrombosis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 310 (0.65%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrial flutter			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure			
subjects affected / exposed	7 / 310 (2.26%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Paraesthesia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital haemorrhage			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
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: 0 %

Non-serious adverse events	Enalapril	Sacubitril/valsartan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 310 (46.13%)	168 / 309 (54.37%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Monoclonal gammopathy			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Vascular disorders			

Blood pressure fluctuation			
subjects affected / exposed	2 / 310 (0.65%)	1 / 309 (0.32%)	
occurrences (all)	2	1	
Haematoma			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Circulatory collapse			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 310 (0.32%)	2 / 309 (0.65%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	20 / 310 (6.45%)	43 / 309 (13.92%)	
occurrences (all)	20	45	
Intermittent claudication			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	1 / 310 (0.32%)	3 / 309 (0.97%)	
occurrences (all)	1	3	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Peripheral coldness			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 310 (0.97%)	1 / 309 (0.32%)	
occurrences (all)	3	1	
Chest pain			

subjects affected / exposed	0 / 310 (0.00%)	5 / 309 (1.62%)	
occurrences (all)	0	5	
Chest discomfort			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	6 / 310 (1.94%)	6 / 309 (1.94%)	
occurrences (all)	7	7	
Feeling abnormal			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	2	
Mucosal dryness			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 310 (0.97%)	5 / 309 (1.62%)	
occurrences (all)	3	6	
Pain			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Swelling			

subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	2	0	
Cough			
subjects affected / exposed	10 / 310 (3.23%)	10 / 309 (3.24%)	
occurrences (all)	10	10	
Dyspnoea			
subjects affected / exposed	9 / 310 (2.90%)	10 / 309 (3.24%)	
occurrences (all)	10	11	
Dysphonia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Emphysema			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	

Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Obstructive airways disorder			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Lung disorder			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	2	0	
Pulmonary hypertension			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Libido decreased			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Psychotic disorder			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Restlessness			

subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	2 / 310 (0.65%)	2 / 309 (0.65%)	
occurrences (all)	2	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Blood 25-hydroxycholecalciferol decreased			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	5 / 310 (1.61%)	6 / 309 (1.94%)	
occurrences (all)	5	6	
Blood potassium decreased			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Blood potassium increased			
subjects affected / exposed	4 / 310 (1.29%)	4 / 309 (1.29%)	
occurrences (all)	4	4	
Blood pressure ambulatory decreased			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Blood pressure decreased			
subjects affected / exposed	0 / 310 (0.00%)	3 / 309 (0.97%)	
occurrences (all)	0	3	
Blood pressure increased			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
C-reactive protein increased			

subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Glomerular filtration rate decreased				
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)		
occurrences (all)	0	2		
Glomerular filtration rate increased				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Heart rate decreased				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Heart rate increased				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Hepatic enzyme increased				
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)		
occurrences (all)	0	2		
Laboratory test abnormal				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Liver function test increased				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Platelet count increased				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Red blood cell sedimentation rate increased				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		
Weight decreased				
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)		
occurrences (all)	1	0		
White blood cell count increased				
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)		
occurrences (all)	0	1		

Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	2	
Drug dispensing error			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Foreign body			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	5 / 310 (1.61%)	1 / 309 (0.32%)	
occurrences (all)	5	1	
Hand fracture			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Injury			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Laceration			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	2 / 310 (0.65%)	2 / 309 (0.65%)	
occurrences (all)	2	2	
Pelvic fracture			

subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Underdose			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Atrial fibrillation			
subjects affected / exposed	2 / 310 (0.65%)	4 / 309 (1.29%)	
occurrences (all)	2	4	
Atrial flutter			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Bradycardia			
subjects affected / exposed	3 / 310 (0.97%)	2 / 309 (0.65%)	
occurrences (all)	3	2	
Cardiac failure			
subjects affected / exposed	11 / 310 (3.55%)	7 / 309 (2.27%)	
occurrences (all)	11	8	
Cardiac failure chronic			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	2 / 310 (0.65%)	3 / 309 (0.97%)	
occurrences (all)	2	4	

Sinus bradycardia			
subjects affected / exposed	2 / 310 (0.65%)	1 / 309 (0.32%)	
occurrences (all)	3	1	
Sinus tachycardia			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Supraventricular tachycardia			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	3	0	
Ventricular fibrillation			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	1 / 310 (0.32%)	3 / 309 (0.97%)	
occurrences (all)	1	3	
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	10 / 310 (3.23%)	17 / 309 (5.50%)	
occurrences (all)	11	20	
Dizziness postural			

subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	4 / 310 (1.29%)	2 / 309 (0.65%)	
occurrences (all)	4	2	
Lethargy			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Hypotonia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	3	
Radiculopathy			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	2	
Somnolence			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 310 (0.65%)	2 / 309 (0.65%)	
occurrences (all)	2	2	
Iron deficiency anaemia			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	

Lymphadenopathy			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	1 / 310 (0.32%)	2 / 309 (0.65%)	
occurrences (all)	1	2	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Glaucoma			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Retinal vein occlusion			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 310 (0.00%)	3 / 309 (0.97%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Abdominal pain upper			

subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Aerophagia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Chronic gastritis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 310 (0.32%)	2 / 309 (0.65%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	6 / 310 (1.94%)	8 / 309 (2.59%)	
occurrences (all)	6	10	
Dry mouth			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	3	
Dysphagia			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Large intestine polyp			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 310 (0.65%)	3 / 309 (0.97%)	
occurrences (all)	2	3	
Odynophagia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Rectal ulcer			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	2	
Angioedema			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Blister			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	

Ecchymosis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Hair texture abnormal			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	2	0	
Madarosis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 310 (0.00%)	4 / 309 (1.29%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	2	
Skin ulcer			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Bladder neck obstruction			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Haematuria			

subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Nocturia			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Renal colic			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Renal disorder			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
subjects affected / exposed	3 / 310 (0.97%)	4 / 309 (1.29%)	
occurrences (all)	3	4	
Renal failure			
subjects affected / exposed	0 / 310 (0.00%)	4 / 309 (1.29%)	
occurrences (all)	0	5	
Renal pain			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 310 (1.94%)	4 / 309 (1.29%)	
occurrences (all)	6	5	
Back pain			

subjects affected / exposed	9 / 310 (2.90%)	6 / 309 (1.94%)	
occurrences (all)	9	7	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Limb discomfort			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Mobility decreased			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	3 / 310 (0.97%)	1 / 309 (0.32%)	
occurrences (all)	3	1	
Myalgia			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Osteoarthritis			
subjects affected / exposed	1 / 310 (0.32%)	2 / 309 (0.65%)	
occurrences (all)	1	2	
Osteochondrosis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Osteopenia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	2	0	
Rheumatoid arthritis			

subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Spinal column stenosis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Spinal osteoarthritis			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	2	0	
Spinal pain			
subjects affected / exposed	0 / 310 (0.00%)	3 / 309 (0.97%)	
occurrences (all)	0	3	
Tendon pain			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 310 (0.65%)	6 / 309 (1.94%)	
occurrences (all)	2	7	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Chlamydial infection			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	

Folliculitis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	2	0	
Herpes simplex			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	8 / 310 (2.58%)	8 / 309 (2.59%)	
occurrences (all)	8	8	
Oesophageal candidiasis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis acute			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	

Respiratory tract infection			
subjects affected / exposed	2 / 310 (0.65%)	1 / 309 (0.32%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	2	
Tracheobronchitis			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 310 (0.65%)	0 / 309 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	3 / 310 (0.97%)	3 / 309 (0.97%)	
occurrences (all)	3	3	
Viral infection			
subjects affected / exposed	1 / 310 (0.32%)	3 / 309 (0.97%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 310 (0.65%)	1 / 309 (0.32%)	
occurrences (all)	2	1	
Dehydration			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	2	
Diabetes mellitus			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 310 (0.32%)	0 / 309 (0.00%)	
occurrences (all)	1	0	
Gout			

subjects affected / exposed	1 / 310 (0.32%)	3 / 309 (0.97%)	
occurrences (all)	1	3	
Hypercalcaemia			
subjects affected / exposed	0 / 310 (0.00%)	2 / 309 (0.65%)	
occurrences (all)	0	3	
Hyperkalaemia			
subjects affected / exposed	11 / 310 (3.55%)	22 / 309 (7.12%)	
occurrences (all)	11	22	
Hyperuricaemia			
subjects affected / exposed	1 / 310 (0.32%)	1 / 309 (0.32%)	
occurrences (all)	1	1	
Hyponatraemia			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 310 (0.00%)	1 / 309 (0.32%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2016	Amendment 1, issued before trial initiation, was introduced as a consequence of feedback and specific requirements from Health Authorities. In summary, these requirements were put in place to detail the potential risk of interaction between specific antidiabetic medication and both the comparator and investigational medicinal product. Furthermore, a precision of specific exclusion criteria were given (26 and 32), by which prohibited concomitant medication and the need for ECG was further specified. In addition, patients eligible for re-screening in the study were further specified as well as further guidance was provided for the eligibility and potential use of the unscheduled visits between set visits. The alert criteria to kidney function were refined in Appendix 16.1.1-Protocol-Appendix 3 where the urine events were deleted due to redundancy with serum events as well as Appendix 16.1.1-Protocol-Appendix 6. A precision was also added in the hypothetical terms where the study could be terminated.
18 November 2016	Amendment 2, issued also before trial initiation, was introduced due to a specific requirement from Health Authorities. The scope of this amendment was to change specific criteria for when patients were found to be eligible for re-screening in this study. Implementation of this amendment increased the precision of patients re-screened and optimized the recruitment of the patients of interest of this study.
02 February 2018	Amendment 3, issued when recruitment was complete, was introduced as a consequence to the realization that combining specific visit windows could allow a mismatch in number of days between visits and number of available study drug. In addition, we added a precision to the dosing level ranges to avoid any ambiguity and lastly, an additional method for imputing missing data was added. Implementation of this amendment secured that the study patients had sufficient study drug throughout the study regardless of how their study visits were constructed within the new visit windows given. Additionally, adding a new method for imputing the missing data allowed better utilization of data which was not complete but useful.
11 April 2018	Amendment 4 issued on 11-Sep-2018, when recruitment was complete and last patient last visit was achieved (11-Apr-2018) but before data base lock and unblinding the patients. The amendment was introduced as a consequence of new and previously unavailable key data regarding the use of accelerometry as a clinical endpoint in trials concerning HF patients and new positioning from the Committee for Medicinal Products for Human Use (CHMP) at the EMA on the use of 6MWT in HF studies (CHMP, 2017).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported