



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 | v2 (current) |
| This version publication date | 23 October 2019 |
| First version publication date | 27 April 2019 |
| Version creation reason | |

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 | Belgium: 14 |
| Country: Number of subjects enrolled | Bulgaria: 22 |
| 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 daily: 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 daily: 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 | 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 | |

| 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 | Investigator, Assessor, Subject |
| 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 daily: 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 daily: 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 received at 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 received at 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 | 302 | | |
| Units: meters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (FAS)(n=301,300) | 365.37 (± 108.18) | 371.08 (± 104.41) | | |
| Week 12 (FAS)(n=292,284) | 395.80 (± 113.11) | 395.33 (± 105.94) | | |
| Chge from BL at Week 12 (FAS)(n=291,282) | 31.57 (± 67.35) | 24.89 (± 51.64) | | |
| Baseline (FAS without AE/SAE)(n=289,292) | 364.72 (± 106.86) | 371.18 (± 105.13) | | |
| Week 12 (FAS without AE/SAE)(n=283,277) | 399.31 (± 110.54) | 396.02 (± 106.39) | | |
| Chge from BL@Wk 12(FAS without AE/SAE)(n= 282,275) | 35.75 (± 58.76) | 25.87 (± 51.73) | | |

Statistical analyses

| Statistical analysis title | Change from BL at Week 12 (FAS) |
|--|---|
| Statistical analysis description: Change from BL at Week 12 (FAS) | |
| Comparison groups | LCZ696 (Sacubitril/Valsartan) v Enalapril |
| Number of subjects included in analysis | 604 |
| 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) |
|---|--|
| Statistical analysis description: Change from BL at Week 12 (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 | = 0.0503 ^[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)(n=302,302) | 510.11 (\pm 128.08) | 506.81 (\pm 139.60) | | |
| Week 12 (FAS with MI)(n=302,302) | 479.69 (\pm 124.23) | 487.53 (\pm 126.84) | | |
| Chge from BL at Wk 12 (FAS with MI)(n=302,302) | -30.42 (\pm 102.55) | -19.28 (\pm 104.44) | | |
| Baseline (FAS with LOCF)(n=259,257) | 512.07 (\pm 126.37) | 505.31 (\pm 129.74) | | |
| Week 12 (FAS with LOCF)(n=253,256) | 489.43 (\pm 127.36) | 490.09 (\pm 127.82) | | |
| Chge from BL@Wk 12 (FAS with LOCF)(n=253,256) | -21.88 (\pm 68.55) | -15.41 (\pm 74.45) | | |
| Baseline (FAS without MI/LOCF)(n=259,257) | 512.07 (\pm 126.37) | 505.31 (\pm 129.74) | | |

| | | | | |
|--|------------------------|------------------------|--|--|
| Week 12 (FAS without MI/LOCF)(n=234,216) | 479.81 (\pm 122.45) | 486.85 (\pm 128.70) | | |
| Chge from BL@Wk 12(FAS without MI/LOCF)(n=203,194) | -25.14 (\pm 69.11) | -20.51 (\pm 72.52) | | |

Statistical analyses

| Statistical analysis title | Change from BL at Week 12 (FAS with MI) |
|---|---|
| Statistical analysis description: | |
| 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 with LOCF) |
|---|---|
| Statistical analysis description: | |
| 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 ^[4] |
| 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:

[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 without MI/LOCF) |
| Statistical analysis description: 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 ^[5] |
| 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:

[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: Number and Percentage of Participants with improved performance (≥ 30 m) in the Six Minute Walk Test (6MWT) - FAS

| | |
|--|---|
| End point title | Number and Percentage of Participants 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 |
| Statistical analysis description: 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: Number and Percentage of Participants with improved performance (≥ 30 m) in the Six Minute Walk Test (6MWT) - FAS subset without AE/SAE

| | |
|--|---|
| End point title | Number and Percentage of Participants 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 |
| Statistical analysis description: 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: Number and Percentage of Participants with improved performance (≥ 30 m) in the 6MWT which walked equal to or less than 300 meters at Baseline - FAS

| | |
|--|--|
| End point title | Number and Percentage of Participants 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 |
| Statistical analysis description: 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: Number and Percentage of Participants 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 | Number and Percentage of Participants 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 |
| Statistical analysis description: 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: Number and Percentage of Participants with improved performance (≥ 30 m) in the 6MWT which walked 100-450 meters at Baseline - FAS

| | |
|--|--|
| End point title | Number and Percentage of Participants 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 |
| Statistical analysis description: 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: Number and Percentage of Participants with improved performance (≥ 30 m) in the 6MWT which walked 100-450 meters at Baseline - FAS subset without AE/SAE

| | |
|--|--|
| End point title | Number and Percentage of Participants 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 | 231 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| No | 103 | 115 | | |
| Yes | 122 | 105 | | |
| Missing | 5 | 11 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | FAS subset without AE/SAE |
| Statistical analysis description: FAS subset without AE/SAE | |
| Comparison groups | LCZ696 (Sacubitril/Valsartan) v Enalapril |
| Number of subjects included in analysis | 461 |
| 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 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 | 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)(n=301,300) | 365.37 (± 108.18) | 371.08 (± 104.41) | | |
| Week 4 (FAS)(n=295,289) | 385.22 (± 110.55) | 385.02 (± 109.92) | | |

| | | | | |
|---|-------------------|-------------------|--|--|
| Chge from BL at Wk 4 (FAS)(n=295,287) | 19.13 (± 49.16) | 13.72 (± 51.39) | | |
| Week 8 (FAS)(n=291,284) | 395.28 (± 112.05) | 391.72 (± 108.99) | | |
| Chge from BL at Wk 8 (FAS)(n=290,282) | 28.72 (± 57.99) | 21.15 (± 52.75) | | |
| Baseline (FAS without AE/SAE)(n=289,292) | 364.72 (± 106.86) | 371.18 (± 105.13) | | |
| Week 4 (FAS without AE/SAE)(n=284,283) | 384.58 (± 107.69) | 385.92 (± 110.81) | | |
| Chge from BL@Wk 4(FAS without AE/SAE)(n=284,281) | 18.91 (± 49.63) | 14.45 (± 51.48) | | |
| Week 8 (FAS without AE/SAE)(n=280,278) | 396.64 (± 110.65) | 391.82 (± 109.72) | | |
| Chge from BL@Wk 8 (FAS without AE/SAE)(n=279,276) | 30.38 (± 57.07) | 21.51 (± 52.99) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL at Week 4 (FAS) |
| Statistical analysis description: 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) |
| Statistical analysis description: 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) |
| Statistical analysis description: 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) |
| Statistical analysis description: 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: Number and Percentage of Participants who show increased levels ($\geq 10\%$ increase) of non sedentary daytime physical activity at Week 12 compared to Baseline

| | |
|-----------------|--|
| End point title | Number and Percentage of Participants who show increased levels ($\geq 10\%$ 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 average 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 |
| Statistical analysis description: | |
| Increased levels (>= 10% increase) of non sedentary daytime physical activity 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: Number and Percentage of Participants achieving PGA Score at Weeks 4, 8 and 12

| | |
|--|--|
| End point title | Number and Percentage of Participants 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 | 2 | 3 | | |
| 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 |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | LCZ696 (Sacubitril/Valsartan) v Enalapril |
| Number of subjects included in analysis | 604 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0516 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 12 |
| Statistical analysis description: | |
| 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 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Week 8 |
| Statistical analysis description: | |
| 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 |

Secondary: Number and Percentage of Participants with improved symptoms of Heart Failure as assessed by Patient Global Assessment (PGA)

| | |
|-----------------|--|
| End point title | Number and Percentage of Participants 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 |
|----------------------------|--------|

Statistical analysis description:

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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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(n=259,257) | 512.07 (± 126.37) | 505.31 (± 129.74) | | |
| Week 1(n=290,292) | 527.34 (± 129.54) | 509.28 (± 131.75) | | |
| Change from BL at Week 1(n=250,250) | 22.60 (± 62.33) | 9.88 (± 50.17) | | |
| Week 2(n=285,292) | 531.19 (± 133.89) | 508.70 (± 133.69) | | |
| Change from BL at Week 2(n=247,250) | 22.80 (± 70.25) | 6.19 (± 55.14) | | |
| Week 3(n=275,282) | 525.98 (± 126.66) | 513.63 (± 130.58) | | |
| Change from BL at Week 3(n=238,241) | 13.55 (± 66.74) | 6.40 (± 62.63) | | |
| Week 4(n=273,275) | 519.45 (± 133.21) | 503.25 (± 139.48) | | |
| Change from BL at Week 4(n=236,234) | 11.99 (± 60.10) | -5.35 (± 72.35) | | |
| Week 5(n=241,220) | 507.46 (± 129.31) | 501.70 (± 138.78) | | |
| Change from BL at Week 5(n=212,190) | 1.77 (± 71.74) | -10.95 (± 81.39) | | |
| Week 6(n=232,214) | 504.15 (± 131.05) | 500.39 (± 136.08) | | |
| Change from BL at Week 6(n=205,185) | -0.44 (± 76.32) | -7.91 (± 69.71) | | |
| Week 7(n=230,215) | 495.06 (± 127.80) | 503.46 (± 139.69) | | |
| Change from BL at Week 7(n=202,187) | -10.35 (± 76.94) | -6.54 (± 75.77) | | |
| Week 8(n=230,213) | 497.62 (± 130.56) | 496.45 (± 139.12) | | |
| Change from BL at Week 8(n=202,186) | -9.49 (± 79.10) | -9.21 (± 75.23) | | |
| Week 9(n=235,222) | 496.74 (± 128.90) | 497.24 (± 131.02) | | |
| Change from BL at Week 9(n=205,196) | -10.09 (± 69.93) | -10.75 (± 75.82) | | |
| Week 10(n=239,219) | 495.53 (± 130.97) | 500.88 (± 138.35) | | |
| Change from BL at Week 10(n=207,194) | -9.48 (± 80.47) | -7.52 (± 77.12) | | |
| Week 11(n=232,214) | 492.28 (± 127.19) | 495.14 (± 135.54) | | |
| Change from BL at Week 11(n=201,192) | -12.93 (± 74.12) | -11.64 (± 75.35) | | |
| Week 12(n=232,214) | 492.28 (± 127.19) | 495.14 (± 135.54) | | |
| Change from BL at Week 12(n=201,192) | -12.93 (± 74.12) | -11.64 (± 75.35) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL at Week 1 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: | |
| 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 |
| Statistical analysis description: | |
| 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 7 |
| Statistical analysis description: | |
| 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 8 |
| Statistical analysis description: | |
| 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 9 |
|-----------------------------------|--------------------------|

Statistical analysis description:

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 10

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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(n=259,257) | 512.07 (\pm 126.37) | 505.31 (\pm 129.74) | | |
| Weeks 0 to 2(n=286,292) | 529.63 (\pm 129.31) | 509.02 (\pm 129.97) | | |
| Change from BL at Week 2(n=248,250) | 22.88 (\pm 60.90) | 8.06 (\pm 45.65) | | |
| Weeks 2 to 4(n=275,279) | 522.30 (\pm 126.68) | 508.57 (\pm 131.41) | | |
| Change from BL at Week 4(n=238,238) | 12.04 (\pm 54.84) | 0.55 (\pm 60.23) | | |
| Weeks 4 to 6(n=236,216) | 505.54 (\pm 127.40) | 500.49 (\pm 135.70) | | |
| Change from BL at Week 6(n=206,186) | 0.21 (\pm 68.47) | -10.86 (\pm 72.76) | | |
| Weeks 6 to 8(n=231,213) | 495.94 (\pm 124.78) | 500.92 (\pm 135.26) | | |
| Change from BL at Week 8(n=203,186) | -10.11 (\pm 71.75) | -7.62 (\pm 69.96) | | |
| Weeks 8 to 10(n=240,221) | 496.57 (\pm 126.68) | 497.02 (\pm 132.96) | | |
| Change from BL at Week 10(n=209,195) | -8.44 (\pm 68.35) | -8.75 (\pm 71.50) | | |
| Weeks 10 to 12(n=226,210) | 483.20 (\pm 121.43) | 493.41 (\pm 130.00) | | |
| Change from BL at Week 12(n=196,188) | -21.17 (\pm 68.77) | -13.93 (\pm 72.85) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL at Week 2 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 7 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(n=259,257) | 251.94 (\pm 50.54) | 247.30 (\pm 58.70) | | |
| Week 1(n=290,292) | 263.17 (\pm 55.85) | 251.37 (\pm 58.13) | | |
| Change from BL at Week 1(n=250,250) | 14.10 (\pm 31.15) | 6.28 (\pm 27.98) | | |
| Week 2(n=285,292) | 262.42 (\pm 55.12) | 248.33 (\pm 57.81) | | |
| Change from BL at Week 2(n=247,250) | 10.91 (\pm 36.10) | 1.58 (\pm 28.80) | | |

| | | | | |
|--------------------------------------|------------------|------------------|--|--|
| Week 3(n=275,282) | 261.80 (± 52.68) | 251.12 (± 57.48) | | |
| Change from BL at Week 3(n=238,241) | 9.68 (± 33.10) | 3.61 (± 31.85) | | |
| Week 4(n=273,275) | 256.10 (± 52.61) | 246.97 (± 58.06) | | |
| Change from BL at Week 4(n=236,234) | 5.14 (± 31.12) | -1.77 (± 33.49) | | |
| Week 5(n=241,220) | 253.98 (± 54.75) | 243.71 (± 59.17) | | |
| Change from BL at Week 5(n=212,190) | 2.71 (± 37.90) | -5.77 (± 37.14) | | |
| Week 6(n=232,214) | 252.10 (± 56.73) | 244.25 (± 57.33) | | |
| Change from BL at Week 6(n=205,185) | 1.08 (± 38.80) | -4.72 (± 36.44) | | |
| Week 7(n=230,215) | 251.02 (± 52.09) | 244.85 (± 57.32) | | |
| Change from BL at Week 7(n=202,187) | -0.88 (± 38.88) | -3.18 (± 37.27) | | |
| Week 8(n=230,213) | 251.46 (± 52.21) | 245.02 (± 59.31) | | |
| Change from BL at Week 8(n=202,186) | -1.71 (± 38.69) | -2.41 (± 36.53) | | |
| Week 9(n=235,222) | 250.04 (± 52.64) | 254.84 (± 56.31) | | |
| Change from BL at Week 9(n=205,196) | -2.54 (± 35.74) | -4.52 (± 37.14) | | |
| Week 10(n=239,219) | 248.33 (± 54.44) | 245.62 (± 58.69) | | |
| Change from BL at Week 10(n=207,194) | -3.43 (± 42.11) | -2.65 (± 36.76) | | |
| Week 11(n=232,214) | 248.19 (± 53.09) | 244.83 (± 59.77) | | |
| Change from BL at Week 11(n=201,192) | -3.86 (± 39.67) | -3.13 (± 34.23) | | |
| Week 12(n=183,173) | 239.30 (± 52.76) | 243.63 (± 56.92) | | |
| Change from BL at Week 12(n=161,157) | -11.98 (± 42.07) | -6.55 (± 35.79) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL at Week 1 |
| Statistical analysis description: 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 |
|-----------------------------------|--------------------------|

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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 7

Statistical analysis description:

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 8

Statistical analysis description:

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 9

Statistical analysis description:

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 10

Statistical analysis description:

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 11

Statistical analysis description:

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 12

Statistical analysis description:

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 7 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(n=259,257) | 260.13 (± 110.94) | 258.01 (± 111.73) | | |
| Week 1(n=290,292) | 264.16 (± 109.31) | 257.92 (± 111.47) | | |
| Change from BL at Week 1(n=250,250) | 8.50 (± 45.86) | 3.60 (± 39.79) | | |
| Week 2(n=285,292) | 268.77 (± 114.83) | 260.37 (± 116.00) | | |
| Change from BL at Week 2(n=247,250) | 11.89 (± 50.98) | 4.61 (± 45.53) | | |
| Week 3(n=275,282) | 264.19 (± 108.10) | 262.51 (± 111.15) | | |
| Change from BL at Week 3(n=238,241) | 3.87 (± 49.53) | 2.80 (± 51.23) | | |
| Week 4(n=273,275) | 263.35 (± 114.86) | 256.28 (± 115.82) | | |
| Change from BL at Week 4(n=236,234) | 6.85 (± 43.45) | -3.58 (± 56.76) | | |
| Week 5(n=241,220) | 253.48 (± 108.52) | 257.99 (± 115.65) | | |
| Change from BL at Week 5(n=212,190) | -0.93 (± 51.57) | -5.18 (± 66.01) | | |
| Week 6(n=232,214) | 252.05 (± 108.75) | 256.14 (± 115.35) | | |
| Change from BL at Week 6(n=205,185) | -1.52 (± 55.23) | -3.19 (± 54.72) | | |
| Week 7(n=230,215) | 244.04 (± 105.32) | 258.61 (± 118.51) | | |
| Change from BL at Week 7(n=202,187) | -9.47 (± 57.67) | -3.35 (± 56.28) | | |
| Week 8(n=230,213) | 246.16 (± 109.03) | 251.42 (± 113.84) | | |
| Change from BL at Week 8(n=202,186) | -7.78 (± 57.13) | -6.80 (± 57.90) | | |
| Week 9(n=235,222) | 246.70 (± 106.78) | 251.40 (± 108.51) | | |
| Change from BL at Week 9(n=205,196) | -7.55 (± 54.98) | -6.23 (± 57.68) | | |
| Week 10(n=239,219) | 247.20 (± 107.41) | 255.26 (± 116.88) | | |
| Change from BL at Week 10(n=207,194) | -6.03 (± 57.08) | -4.86 (± 59.50) | | |
| Week 11(n=232,214) | 244.09 (± 104.33) | 250.31 (± 113.81) | | |
| Change from BL at Week 11(n=201,192) | -9.07 (± 51.95) | -8.51 (± 61.45) | | |
| Week 12(n=183,173) | 237.15 (± 100.32) | 248.08 (± 113.51) | | |
| Change from BL at Week 12(n=161,157) | -20.52 (± 58.37) | -11.57 (± 64.90) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL at Week 1 |
| Statistical analysis description: | |
| 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 |
| Statistical analysis description: | |
| 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 |
| Statistical analysis description: | |
| 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 |
| Statistical analysis description: | |
| 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 |
|-----------------------------------|--------------------------|

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

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(n=264,263) | 3616.87 (\pm 964.92) | 3528.56 (\pm 993.10) | | |
| Week 1(n=290,292) | 3676.46 (\pm 923.85) | 3560.10 (\pm 916.16) | | |
| Change from BL at Week 1(n=255,256) | 103.29 (\pm 509.20) | 82.48 (\pm 588.19) | | |
| Week 2(n=285,292) | 3691.24 (\pm 953.03) | 3557.71 (\pm 940.60) | | |
| Change from BL at Week 2(n=251,256) | 76.23 (\pm 563.79) | 52.38 (\pm 600.08) | | |
| Week 3(n=275,282) | 3668.25 (\pm 894.91) | 3580.54 (\pm 922.70) | | |
| Change from BL at Week 3(n=242,246) | 25.28 (\pm 571.36) | 34.56 (\pm 663.68) | | |
| Week 4(n=273,275) | 3608.39 (\pm 936.87) | 3482.15 (\pm 991.15) | | |
| Change from BL at Week 4(n=240,239) | 5.10 (\pm 497.55) | -56.23 (\pm 748.35) | | |
| Week 5(n=241,220) | 3488.43 (\pm 944.87) | 3458.65 (\pm 973.75) | | |
| Change from BL at Week 5(n=214,196) | -116.74 (\pm 607.31) | -79.18 (\pm 817.71) | | |
| Week 6(n=232,214) | 3519.12 (\pm 922.58) | 3489.15 (\pm 962.55) | | |
| Change from BL at Week 6(n=207,191) | -72.08 (\pm 569.61) | -21.73 (\pm 724.96) | | |
| Week 7(n=230,215) | 3444.52 (\pm 892.15) | 3502.67 (\pm 977.43) | | |
| Change from BL at Week 7(n=205,192) | -143.38 (\pm 605.25) | -36.18 (\pm 709.43) | | |
| Week 8(n=230,213) | 3466.82 (\pm 936.51) | 3457.74 (\pm 993.56) | | |
| Change from BL at Week 8(n=205,190) | -130.59 (\pm 631.30) | -59.92 (\pm 716.74) | | |
| Week 9(n=235,222) | 3470.69 (\pm 913.06) | 3447.28 (\pm 932.67) | | |
| Change from BL at Week 9(n=208,199) | -131.08 (\pm 549.54) | -108.48 (\pm 719.58) | | |
| Week 10(n=239,219) | 3444.77 (\pm 947.18) | 3489.68 (\pm 964.08) | | |

| | | | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Change from BL at Week 10(n=212,197) | -119.41 (± 648.17) | -68.93 (± 711.22) | | |
| Week 11(n=232,214) | 3406.56 (± 910.84) | 3436.96 (± 971.78) | | |
| Change from BL at Week 11(n=205,194) | -170.14 (± 632.53) | -120.35 (± 707.11) | | |
| Week 12(n=183,173) | 3093.96 (± 913.14) | 3234.90 (± 991.50) | | |
| Change from BL at Week 12(n=165,158) | -506.82 (± 792.71) | -339.15 (± 786.06) | | |

Statistical analyses

| Statistical analysis title | Change from BL at Week 1 |
|---|---|
| Statistical analysis description: 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 |
|---|---|
| Statistical analysis description: 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 |
|---|---|
| Statistical analysis description: 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 |
| Statistical analysis description: | |
| 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 |
| Statistical analysis description: | |
| 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 |
| Statistical analysis description: | |
| 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 7 |
| Statistical analysis description: | |
| 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 8 |
|-----------------------------------|--------------------------|

Statistical analysis description:

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 9

Statistical analysis description:

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 10

Statistical analysis description:

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 11

Statistical analysis description:

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 12

Statistical analysis description:

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, 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 (n=264,263) | 1773.14 (± 392.22) | 1721.50 (± 452.26) | | |
| Week 1 (n=290,292) | 1834.71 (± 400.46) | 1757.76 (± 407.14) | | |
| Change from BL at Week 1 (n=255,256) | 81.84 (± 255.91) | 53.74 (± 282.22) | | |
| Week 2 (n=285,292) | 1823.86 (± 396.55) | 1736.64 (± 407.45) | | |
| Change from BL at Week 2 (n=251,256) | 46.26 (± 301.74) | 17.26 (± 280.12) | | |
| Week 3 (n=275,282) | 1826.38 (± 376.72) | 1751.95 (± 410.11) | | |
| Change from BL at Week 3 (n=242,246) | 46.05 (± 281.11) | 24.88 (± 313.52) | | |
| Week 4 (n=273,275) | 1778.88 (± 372.86) | 1707.68 (± 410.73) | | |
| Change from BL at Week 4 (n=240,239) | 9.17 (± 275.92) | -18.74 (± 346.02) | | |
| Week 5 (n=241,220) | 1745.87 (± 406.21) | 1683.08 (± 429.50) | | |
| Change from BL at Week 5 (n=214,196) | -36.66 (± 307.01) | -37.98 (± 369.53) | | |
| Week 6 (n=232,214) | 1759.09 (± 397.67) | 1701.89 (± 405.01) | | |

| | | | | |
|--|--------------------|--------------------|--|--|
| Change from BL at Week 6 (n=207,191) | -17.85 (± 290.75) | -16.56 (± 343.51) | | |
| Week 7 (n=230,215) | 1747.03 (± 366.43) | 1702.58 (± 399.11) | | |
| Change from BL at Week 7 (n=205, 192) | -32.03 (± 307.16) | -17.71 (± 322.33) | | |
| Week 8 (n=230,213) | 1750.02 (± 377.35) | 1705.09 (± 424.99) | | |
| Change from BL at Week 8 (n=205,190) | -37.50 (± 323.19) | -17.49 (± 318.83) | | |
| Week 9 (n=235,222) | 1746.73 (± 375.07) | 1706.26 (± 407.89) | | |
| Change from BL at Week 9 (n=208,199) | -36.47 (± 289.67) | -43.21 (± 341.30) | | |
| Week 10 (n=239,219) | 1724.72 (± 395.95) | 1712.55 (± 412.82) | | |
| Change from BL at Week 10 (n=212,197) | -46.95 (± 339.81) | -22.01 (± 314.65) | | |
| Week 11 (n=232,214) | 1717.08 (± 386.33) | 1697.81 (± 429.44) | | |
| Change from BL at Week 11 (n=205, 194) | -60.08 (± 319.85) | -40.52 (± 313.76) | | |
| Week 12 (n=183,173) | 1559.62 (± 428.02) | 1607.33 (± 449.83) | | |
| Change from BL at Week 12 (n=165,158) | -210.49 (± 390.17) | -144.96 (± 339.29) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL at Week 1 |
| Statistical analysis description: | |
| 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 2 |
| Statistical analysis description: | |
| 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 3 |
| Statistical analysis description: 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 4 |
| Statistical analysis description: 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 5 |
| Statistical analysis description: 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 6 |
| Statistical analysis description: 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 |
|-----------------------------------|--------------------------|

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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 (n=264,263) | 1843.73 (± 830.30) | 1807.07 (± 815.89) | | |
| Week 1 (n=290,292) | 1841.76 (± 769.54) | 1802.34 (± 775.36) | | |
| Change from BL at Week 1 (n=255,256) | 21.45 (± 373.16) | 28.75 (± 404.20) | | |
| Week 2 (n=285, 292) | 1867.37 (± 806.56) | 1821.07 (± 813.27) | | |

| | | | | |
|---------------------------------------|--------------------|--------------------|--|--|
| Change from BL at Week 2 (n=251,256) | 29.97 (± 383.31) | 35.13 (± 432.43) | | |
| Week 3 (n=275,282) | 1841.87 (± 755.88) | 1828.59 (± 777.65) | | |
| Change from BL at Week 3 (n=242,246) | -20.77 (± 425.19) | 9.68 (± 458.99) | | |
| Week 4 (n=273,275) | 1829.51 (± 801.93) | 1774.46 (± 815.93) | | |
| Change from BL at Week 4 (n=240,239) | -4.07 (± 344.29) | -37.49 (± 506.27) | | |
| Week 5 (n=241,220) | 1742.56 (± 767.53) | 1775.57 (± 798.92) | | |
| Change from BL at Week 5 (n=214,196) | -80.08 (± 423.07) | -41.20 (± 577.49) | | |
| Week 6 (n=232,214) | 1760.03 (± 763.64) | 1787.26 (± 810.30) | | |
| Change from BL at Week 6 (n=207,191) | -54.23 (± 416.05) | -5.17 (± 509.74) | | |
| Week 7 (n=230,215) | 1697.49 (± 732.18) | 1800.09 (± 829.37) | | |
| Change from BL at Week 7 (n=205,192) | -111.35 (± 438.85) | -18.47 (± 505.11) | | |
| Week 8 (n=230,213) | 1716.80 (± 769.31) | 1752.65 (± 802.46) | | |
| Change from BL at Week 8 (n=205,190) | -93.09 (± 429.65) | -42.43 (± 522.80) | | |
| Week 9 (n=235,222) | 1723.96 (± 750.60) | 1741.02 (± 757.26) | | |
| Change from BL at Week 9 (n=208,199) | -94.81 (± 407.63) | -65.27 (± 492.38) | | |
| Week 10 (n=239,219) | 1720.06 (± 760.72) | 1777.14 (± 811.27) | | |
| Change from BL at Week 10 (n=212,197) | -72.46 (± 442.80) | -46.92 (± 514.49) | | |
| Week 11 (n=232,214) | 1689.48 (± 731.77) | 1739.15 (± 803.36) | | |
| Change from BL at Week 11 (n=205,194) | -110.06 (± 432.47) | -79.83 (± 516.05) | | |
| Week 12 (n=183,173) | 1534.35 (± 678.12) | 1627.57 (± 778.70) | | |
| Change from BL at Week 12 (n=165,158) | -296.33 (± 525.81) | -194.19 (± 564.53) | | |

Statistical analyses

| Statistical analysis title | Change from BL at Week 1 |
|---|---|
| Statistical analysis description: | |
| 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 |
| Statistical analysis description: 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 7 |
| Statistical analysis description: 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 8 |
| Statistical analysis description: 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 9 |
| Statistical analysis description: 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 10 |
| Statistical analysis description: 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 11 |
| Statistical analysis description: 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 12 |
| Statistical analysis description: 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 (n=259,257) | 189.08 (± 67.75) | 182.52 (± 60.09) | | |
| Week 2 (n=286,292) | 193.54 (± 77.30) | 184.46 (± 59.49) | | |
| Change from BL at Week 2 (n=247,250) | 6.18 (± 46.72) | 3.52 (± 32.16) | | |
| Week 4 (n=273,275) | 191.86 (± 80.21) | 181.11 (± 61.75) | | |
| Change from BL at Week 4 (n=236,234) | 5.47 (± 50.93) | -0.23 (± 40.44) | | |
| Week 6 (n=232,214) | 191.21 (± 77.38) | 181.11 (± 55.07) | | |
| Change from BL at Week 6 (n=205,185) | 2.69 (± 42.51) | -1.02 (± 38.82) | | |
| Week 8 (n=230,213) | 183.96 (± 70.54) | 180.92 (± 57.28) | | |
| Change from BL at Week 8 (n=202,186) | -2.71 (± 41.43) | -0.22 (± 38.05) | | |
| Week 12 (n=183,173) | 184.42 (± 67.09) | 180.44 (± 55.36) | | |
| Change from BL at Week 12 (n=161,157) | -1.07 (± 49.32) | -2.45 (± 39.15) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL at Week 2 |
| Statistical analysis description: | |
| 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 |
|----------------------------|--------------------------|

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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

Statistical analysis description:

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' 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 | Sacubitril/valsartan |
|-----------------------|----------------------|

Reporting group description:

Sacubitril/valsartan

| | |
|-----------------------|-----------|
| Reporting group title | Enalapril |
|-----------------------|-----------|

Reporting group description:

Enalapril

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

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

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

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

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

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

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

Frequency threshold for reporting non-serious adverse events: 0 %

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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