# Clinical trial results:
# A Phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic HeArt FaiLure with reduced Ejection Fraction (HFrEF) (EMPERIAL – reduced)

## Summary

| | |
|---|---|
| EudraCT number | 2017-004073-14 |
| Trial protocol | ES GR PT PL SE NO IT |
| Global end of trial date | 07 October 2019 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 01 December 2021 |
| First version publication date | 15 October 2020 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1245-0168 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03448419 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Straße 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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 | 04 November 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 September 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the effect of empagliflozin 10 mg vs. placebo on exercise ability using the 6-minute walk test (6MWT) in patients with chronic heart failure (CHF) with reduced left ventricular ejection fraction (LVEF ≤40%). Secondary objectives were to assess patient-reported Outcomes (PRO).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. An independent DMC was formed to monitor patients' safety throughout the conduct of the trial at regular meetings. An independent external CEC adjudicated selected hepatic events and ketoacidosis while blinded to the patient's treatment allocation.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 March 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 12 |
| Country: Number of subjects enrolled | Canada: 17 |
| Country: Number of subjects enrolled | Germany: 63 |
| Country: Number of subjects enrolled | Spain: 52 |
| Country: Number of subjects enrolled | Greece: 37 |
| Country: Number of subjects enrolled | Italy: 27 |
| Country: Number of subjects enrolled | Norway: 20 |
| Country: Number of subjects enrolled | Poland: 101 |
| Country: Number of subjects enrolled | Portugal: 44 |
| Country: Number of subjects enrolled | Sweden: 17 |
| Country: Number of subjects enrolled | United States: 317 |
| Worldwide total number of subjects | 707 |
| EEA total number of subjects | 361 |

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) | 258 |
| From 65 to 84 years | 424 |
| 85 years and over | 25 |

## Subject disposition

### Recruitment

Recruitment details:

Randomised, double-blind, placebo-controlled, parallel-group trial in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF) to evaluate the effect of Empagliflozin versus Placebo on exercise and heart failure symptoms.

### Pre-assignment

Screening details:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

### Period 1

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

Blinding implementation details:

Patients, investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained
blinded with regard to the randomised treatment assignments until after database lock. The randomisation code was kept secret by Clinical Trial Support up to database lock.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

1 film-coated tablet of placebo matching empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%).

| | |
|---|---|
| Arm type | Placebo |
| 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:

1 film-coated tablet of placebo matching empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%).

| | |
|---|---|
| **Arm title** | 10 mg Empagliflozin |

Arm description:

1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%).

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

Dosage and administration details:

1 film-coated tablet of 10 milligram (mg) of Empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction

(LVEF≤40%).

| **Number of subjects in period 1[1]** | Placebo | 10 mg Empagliflozin |
|---|---|---|
| Started | 156 | 156 |
| Treated | 156 | 155 |
| Completed | 143 | 140 |
| Not completed | 13 | 16 |
| Adverse event, serious fatal | 3 | 1 |
| Consent withdrawn by subject | 3 | 1 |
| Withdrawn by Sponsor | - | 1 |
| Adverse event, non-fatal | 7 | 8 |
| Lost to follow-up | - | 2 |
| Patient did not attend all visits | - | 2 |
| Not treated | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 707 subjects were enrolled worldwide and thereof 312 subjects were included in the trial.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| 1 film-coated tablet of placebo matching empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%). | |
| Reporting group title | 10 mg Empagliflozin |
| Reporting group description: | |
| 1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%). | |

| Reporting group values | Placebo | 10 mg Empagliflozin | Total |
|---|---|---|---|
| Number of subjects | 156 | 156 | 312 |
| Age categorical | | | |
| Randomised Set: All subjects that were randomised, regardless of whether treated or not. | | | |
| 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) | 48 | 47 | 95 |
| From 65-84 years | 97 | 106 | 203 |
| 85 years and over | 11 | 3 | 14 |
| Age Continuous | | | |
| Randomised Set: All subjects that were randomised, regardless of whether treated or not. | | | |
| Units: years | | | |
| arithmetic mean | 69.3 | 68.7 | |
| standard deviation | ± 10.6 | ± 9.9 | - |
| Sex: Female, Male | | | |
| Randomised Set: All subjects that were randomised, regardless of whether treated or not. | | | |
| Units: Subjects | | | |
| Female | 45 | 35 | 80 |
| Male | 111 | 121 | 232 |
| Race (NIH/OMB) | | | |
| Randomised Set: All subjects that were randomised, regardless of whether treated or not. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 2 | 1 | 3 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 18 | 24 | 42 |
| White | 133 | 130 | 263 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Ethnicity (NIH/OMB) | | | |

| Randomised Set: All subjects that were randomised, regardless of whether treated or not. | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Hispanic or Latino | 23 | 20 | 43 |
| Not Hispanic or Latino | 132 | 136 | 268 |
| Unknown or Not Reported | 1 | 0 | 1 |

| Exercise capacity as measured by the 6-Minutes-Walking-Test (6MWT) distance at baseline | | | |
|---|---|---|---|
| 6 Minute Walking test measures the distance walked in 6 minutes in standardised conditions at baseline. Randomised Set: All subjects that were randomised, regardless of whether treated or not. | | | |
| Units: Meter | | | |
| median | 309.0 | 306.0 | |
| inter-quartile range (Q1-Q3) | 248.5 to 332.0 | 260.0 to 333.5 | - |

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| 1 film-coated tablet of placebo matching empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%). | |
| Reporting group title | 10 mg Empagliflozin |
| Reporting group description: | |
| 1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%). | |

### Primary: Change from baseline to week 12 in exercise capacity as measured by the 6-Minutes-Walking-Test (6MWT) distance

| End point title | Change from baseline to week 12 in exercise capacity as measured by the 6-Minutes-Walking-Test (6MWT) distance |
|---|---|
| End point description: | |
| Change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions. If repeated 6MWT measurements were available for the same day, the longest distance was used for analysis. Change from baseline was defined as the distance walked in 6 minutes at week 12 minus the baseline value. Baseline value was defined as the last available measurement before start of treatment with randomised study medication. If a subject was present at the visit at week 12 but did not perform the 6MWT, the subject was evaluated as having walked a distance of 0 meter. If no value was available for week 12, an imputed value was used. Patients with missing week 12 data who had no clinical event were ranked below any patient with non-missing data, but above the patients who had clinical events. Patients who died before week 12 were ranked below the patients in all categories above. Randomised Set (RS). | |
| End point type | Primary |
| End point timeframe: | |
| At baseline and at week 12 | |

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156[1] | 156[2] | | |
| Units: Meter (m) | | | | |
| median (inter-quartile range (Q1-Q3)) | 18.0 (-11.5 to 54.0) | 13.5 (-8.0 to 42.0) | | |

Notes:

[1] - RS

[2] - RS

### Statistical analyses

| **Statistical analysis title** | Superiority of Empagliflozin vs. Placebo |
|---|---|
| Statistical analysis description: | |
| H0: There is no difference between the effect of placebo and the effect of empagliflozin. | |
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 312 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4236 |
| Method | Wilcoxon rank test, normal approximation |
| Parameter estimate | Median difference (HL-estimate) |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16 |
| upper limit | 6 |

## Secondary: Change from baseline to week 12 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS)

| | |
|---|---|
| End point title | Change from baseline to week 12 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) |

End point description:

Change from baseline in KCCQ-TSS was defined as the endpoint value at week 12 minus the last available measurement before start of treatment with randomised study medication. The KCCQ is 23 item self-administered questionnaire and comprises 7 domains: physical limitation, symptom frequency, symptom burden, symptom stability, social limitation, self-efficacy and quality of life. Additionally 3 summary scores exist: TSS, clinical summary score, and overall summary score. The scores of the KCCQ domains and summary scores range from 0 to 100, with higher score indicating better outcome. If no questionnaire was available at week 12, an imputed value was used. Patients with missing week 12 data who had no clinical event were ranked below any patient with non-missing data, but above the patients who had clinical events. Patients who died before week 12 were ranked below the patients in all categories above. If no questionnaire was available at baseline, change from baseline was not imputed.

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

End point timeframe:

At baseline and at week 12

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156[3] | 156[4] | | |
| Units: Score on a scale | | | | |
| median (inter-quartile range (Q1-Q3)) | 3.65 (-6.25 to 13.54) | 7.29 (-2.60 to 18.75) | | |

Notes:

[3] - Ranodmised Set (RS)

[4] - Randomised Set (RS)

### Statistical analyses

| **Statistical analysis title** | Superiority of Empagliflozin vs. Placebo |
|---|---|

Statistical analysis description:

H0: There is no difference between the effect of placebo and the effect of empagliflozin.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 312 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0893 |
| Method | Wilcoxon rank test, normal approximation |
| Parameter estimate | Median difference (HL-estimate) |
| Point estimate | 3.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 7.29 |

## Secondary: Change from baseline to week 12 in Chronic Heart Failure Questionnaire Self- Administered Standardized format (CHQ-SAS) dyspnea score

| | |
|---|---|
| End point title | Change from baseline to week 12 in Chronic Heart Failure Questionnaire Self- Administered Standardized format (CHQ-SAS) dyspnea score |

End point description:

Change from baseline in CHQ-SAS was defined as the endpoint value at week 12 minus the last available endpoint value before start of treatment with randomised study medication. The CHQ-SAS evaluates 3 domains: dyspnoea, fatigue, and emotional function. Scores of the domains range from 1 to 7, with higher score indicating better quality of life. If no questionnaire was available at week 12, an imputed value was used. Patients with missing week 12 data who had no clinical event were ranked below any patient with non-missing data, but above the patients who had clinical events. Patients who died before week 12 were ranked below the patients in all categories above. If no questionnaire was available at baseline, change from baseline was not imputed. Subjects in the randomised set (RS) who have no missing values at baseline.

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

End point timeframe:

At baseline and at week 12

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156[5] | 154[6] | | |
| Units: Score on scale | | | | |
| median (confidence interval 95%) | 0.40 (-0.33 to 0.83) | 0.40 (-0.50 to 1.33) | | |

Notes:

[5] - Subjects in the randomised set (RS) who have no missing values at baseline.

[6] - Subjects in the randomised set (RS) who have no missing values at baseline.

### Statistical analyses

| **Statistical analysis title** | Superiority of Empagliflozin vs. Placebo |
|---|---|

Statistical analysis description:

H0: There is no difference between the effect of placebo and the effect of empagliflozin.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 310 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4702 |
| Method | Wilcoxon rank test, normal approximation |
| Parameter estimate | Median Difference (HL-estimate) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.4 |

## Secondary: Change from baseline to week 6 in exercise capacity as measured by the 6-Minutes-Walking-Test (6MWT) distance

| | |
|---|---|
| End point title | Change from baseline to week 6 in exercise capacity as measured by the 6-Minutes-Walking-Test (6MWT) distance |

End point description:

Change from baseline to week 6 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions. Change from baseline was defined as the distance walked in 6 minutes at week 6 minus the baseline value. Baseline value was defined as the last available measurement before start of treatment with randomised study medication.
If a subject was present at the visit at week 6 but did not perform the 6MWT, the subject was evaluated as having walked a distance of 0 meter. If no value was available for week 6, an imputed value was used. Randomised Set (RS): All subjects that were randomised, regardless of whether treated or not.

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

End point timeframe:

At baseline and at week 6

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156[7] | 156[8] | | |
| Units: Meter (m) | | | | |
| median (inter-quartile range (Q1-Q3)) | 7.0 (-10.5 to 39.5) | 9.5 (-12.5 to 32.0) | | |

Notes:

[7] - RS

[8] - RS

### Statistical analyses

| Statistical analysis title | Superiority of Empagliflozin vs. Placebo |
|---|---|

Statistical analysis description:

H0: There is no difference between the effect of placebo and the effect of empagliflozin.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 312 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.983 |
| Method | Wilcoxon rank test, normal approximation |
| Parameter estimate | Median difference (HL-estimate) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9 |
| upper limit | 9 |

## Secondary: Change from baseline to week 12 in Clinical Congestion Score

| | |
|---|---|
| End point title | Change from baseline to week 12 in Clinical Congestion Score |

End point description:

Change from baseline to week 12 in Clinical Congestion score is defined as the score-value at week 12 minus the score-value at baseline. Baseline value was defined as the last available measurement before start of treatment with randomised study medication. The Clinical Congestion score assessed the subjects congestion using a clinician-based outcome assessment of 6 different signs and symptoms: dyspnoea, orthopnoea, fatigue, jugular venous distention (as assessed by the investigator), rales, and oedema. Each category was assessed through a 4-measure questionnaire, which was further converted to a standardised 4-point scale ranging from 0 to 3, which 0 indicating no or fewer symptoms and 3 indicating continous or more symptoms. Mean is adjusted mean. Only subjects in the randomised set (RS) who have baseline and at least one post-baseline value, are included in the analysis.

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

End point timeframe:

At baseline and at week 12

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153[9] | 155[10] | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard error) | -0.30 (± 0.08) | -0.61 (± 0.08) | | |

Notes:

[9] - Only subjects in the randomised set (RS) who have baseline and at least one post-baseline value.

[10] - Only subjects in the randomised set (RS) who have baseline and at least one post-baseline value.

### Statistical analyses

| Statistical analysis title | Effect of Empagliflozin vs Placebo |
|---|---|

Statistical analysis description:

Mixed model repeated measure included treatment-by-visit interaction and baseline value-by-visit interaction as fixed effects. Unstructured covariance structure was used to model within-patient errors.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0053 |
| Method | Mixed Model repeated Measures (MMRM) |
| Parameter estimate | Adjusted mean |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | -0.09 |

## Secondary: Change from baseline to week 12 in Patient Global Impression of Severity (PGI-S) of Heart Failure Symptoms

| | |
|---|---|
| End point title | Change from baseline to week 12 in Patient Global Impression of Severity (PGI-S) of Heart Failure Symptoms |

End point description:

Change from baseline to week 12 in PGI-S of Heart Failure Symptoms. The Patient Global Impression of Severity (PGI-S) of Heart Failure Symptoms is a 1-item questionnaire to assess the patient's impression of symptoms severity, specifically: shortness of breath, fatigue and swelling. The PGI-S asks the Patient to choose one response that best describes how his/her heart failure symptoms, specifically: shortness of breath, fatigue and swelling are now on a 5-point scale, ranging from 'Not at all' (1) to 'Very severe' (5). Number of participants by change in score are reported. Change in score was defined as the number of categories improved/deteriorated from baseline to week 12. Only subjects in the randomised set (RS) who have values at baseline and at week 12 are included in the analysis.

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

End point timeframe:

At baseline and at week 12

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 149[11] | 147[12] | | |
| Units: Subjects | | | | |
| 4 categories improvement | 0 | 0 | | |
| 3 categories improvement | 1 | 1 | | |
| 2 categories improvement | 13 | 14 | | |
| 1 category improvement | 41 | 41 | | |
| No change | 73 | 74 | | |
| 1 category deterioration | 16 | 16 | | |
| 2 categories deterioration | 4 | 1 | | |
| 3 categories deterioration | 1 | 0 | | |
| 4 categories deterioration | 0 | 0 | | |

Notes:

[11] - Only subjects in the randomised set (RS) who have values at baseline and at week 12.

[12] - Only subjects in the randomised set (RS) who have values at baseline and at week 12.

## Statistical analyses

| Statistical analysis title | Effect of Empagliflozin vs Placebo |
|---|---|

Statistical analysis description:

Test on difference in mean treatment scores, based on modified ridit scores.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 296 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6189 |
| Method | Cochran-Mantel-Haenszel test |

## Secondary: Change from baseline to week 12 in Patient Global Impression of Severity (PGI-S) of dyspnoea

| End point title | Change from baseline to week 12 in Patient Global Impression of Severity (PGI-S) of dyspnoea |
|---|---|

End point description:

Change from baseline to week 12 in Patient Global Impression of Severity (PGI-S) of dyspnoea. The PGI-S of Dyspnoea is a 1-item questionnaire designed to assess the participant´s impression of symptom severity, specifically dyspnoea. The PGI-S item asks the participant to choose one response that best describes how his/her dyspnoea is now on a 5-point scale, ranging from 'Not at all' (1) to 'Very severe' (5). Number of subjects by change in score are reported. Change in score was defined as the number of categories improved/deteriorated from baseline to week 12. Only subjects in the randomised set (RS) who have values at baseline and at week 12 are included in the analysis.

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

End point timeframe:

At baseline and at week 12

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 147[13] | 150[14] | | |
| Units: Subjects | | | | |
| 4 categories improvment | 0 | 0 | | |
| 3 categories improvment | 3 | 2 | | |
| 2 categories improvement | 8 | 11 | | |
| 1 category improvement | 38 | 46 | | |
| No change | 83 | 70 | | |
| 1 category deterioration | 13 | 17 | | |
| 2 categories deterioration | 2 | 4 | | |
| 3 categories deterioration | 0 | 0 | | |
| 4 categories deterioration | 0 | 0 | | |

Notes:

[13] - Only subjects in the randomised set (RS) who have values at baseline and at week 12.

[14] - Only subjects in the randomised set (RS) who have values at baseline and at week 12.

## Statistical analyses

| Statistical analysis title | Effect of Empagliflozin vs Placebo |
|---|---|

Statistical analysis description:

Test on difference in mean treatment scores, based on modified ridit scores.

| | |
|---|---|
| Comparison groups | 10 mg Empagliflozin v Placebo |
| Number of subjects included in analysis | 297 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6672 |
| Method | Cochran-Mantel-Haenszel test |

## Secondary: Patient Global Impression of Change (PGI-C) in Heart Failure Symptoms at week 12

| | |
|---|---|
| End point title | Patient Global Impression of Change (PGI-C) in Heart Failure Symptoms at week 12 |

End point description:

The Patient Global Impression of Change (PGI-C) in Heart Failure Symptoms is a 1-item questionnaire to assess the patient's impression of change in heart failure symptoms, specifically: shortness of breath, fatigue, and swelling. The PGI-C asks the patient to choose one Response that best describes the overall change (if any) in his/her heart failure symptoms, specifically: shortness of breath, fatigue, and swelling since he/she started taking the study medication on a 7- category scale ranging from 'Very much better' (+3) to 'Very much worse' (-3). Only subjects in the randomised set (RS) who have week 12 value are included in the analysis.

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

End point timeframe:

At week 12

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 150[15] | 147[16] | | |
| Units: Subjects | | | | |
| Very much worse | 0 | 0 | | |
| Much worse | 3 | 0 | | |
| A little worse | 7 | 5 | | |
| No change | 57 | 51 | | |
| A little better | 40 | 52 | | |
| Much better | 34 | 33 | | |
| Very much better | 9 | 6 | | |

Notes:

[15] - Only subjects in the randomised set (RS) who have week 12 value.

[16] - Only subjects in the randomised set (RS) who have week 12 value.

### Statistical analyses

| **Statistical analysis title** | Effect of Empagliflozin vs Placebo |
|---|---|

Statistical analysis description:

Test on difference in mean treatment scores, based on modified ridit scores.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 297 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5147 |
| Method | Cochran-Mantel-Haenszel test |

## Secondary: Patient Global Impression of Change (PGI-C) in dyspnea at week 12

| | |
|---|---|
| End point title | Patient Global Impression of Change (PGI-C) in dyspnea at week 12 |

End point description:

The PGI-C in Dyspnoea is a 1-item questionnaire designed to assess the patient's Impression of change in dyspnoea. The PGI-C asks the patient to choose one response that best describes the change (if any) in his/her shortness of breath when performing usual activities since he/she started taking the study medication on a 7-category scale ranging from 'Very much better' (+3) to 'Very much worse' (-3). Only subjects in the randomised set (RS) who have week 12 value are included in the analysis.

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

End point timeframe:

At week 12

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 149[17] | 147[18] | | |
| Units: Subjects | | | | |
| Very much worse | 0 | 0 | | |
| Much worse | 2 | 0 | | |
| A little worse | 6 | 3 | | |
| No change | 52 | 49 | | |
| A little better | 45 | 59 | | |
| Much better | 34 | 30 | | |
| Very much better | 10 | 6 | | |

Notes:

[17] - Only subjects in the randomised set (RS) who have week 12 value.

[18] - Only subjects in the randomised set (RS) who have week 12 value.

### Statistical analyses

| Statistical analysis title | Effect of Empagliflozin vs Placebo |
|---|---|

Statistical analysis description:

Test on difference in mean treatment scores, based on modified ridit scores.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 296 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.863 |
| Method | Cochran-Mantel-Haenszel test |

## Secondary: Relative change from baseline to week 12 in N-terminal pro-brain natriuretic peptide (NTproBNP)

| End point title | Relative change from baseline to week 12 in N-terminal pro-brain natriuretic peptide (NTproBNP) |
|---|---|

End point description:

Relative change from baseline to week 12 in N-terminal pro-brain natriuretic peptide (NTproBNP). Baseline value was defined as the mean of all available measurements from the screening visit until start of treatment with randomised study medication. Only subjects in the randomised set (RS), who had values at baseline and at least one post baseline value are included in the analysis.

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

End point timeframe:

Within 3 weeks prior to treatment start and at Week 12

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153[19] | 155[20] | | |
| Units: Ratio of adjusted geometric means | | | | |
| number (confidence interval 95%) | 0.98 (0.90 to 1.06) | 0.89 (0.82 to 0.97) | | |

Notes:

[19] - Subjects in the randomised set, who have values at baseline and at least on post baseline value.

[20] - Subjects in the randomised set, who have values at baseline and at least one post-baseline value.

### Statistical analyses

| **Statistical analysis title** | Effect of Empagliflozin vs Placebo |
|---|---|

Statistical analysis description:

The endpoint ‘relative change from baseline in NT-proBNP at Week 12’ (after log-transformation) was evaluated using an MMRM analysis over time with baseline log-transformed NT-proBNP-by-visit interaction and visit-by-treatment interaction as covariates.Unstructured covariance structure was used to model within-patient errors.

| Comparison groups | Placebo v 10 mg Empagliflozin |
|---|---|
| Number of subjects included in analysis | 308 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.141 |
| Method | Mixed Model repeated Measures (MMRM) |
| Parameter estimate | Adjusted geometric mean ratio |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.03 |

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

From first intake of study medication, until 7 days after last intake of study medication, up to 91 days.

Adverse event reporting additional description:

Treated Set: All participants wo were treated with at least 1 dose of the study medication.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | 10 mg Empagliflozin |

Reporting group description:

1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%).

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

1 film-coated tablet of placebo matching empagliflozin was administered orally once daily for 12 weeks in subjects with chronic Heart Failure (CHF) with reduced left ventricular ejection fraction (LVEF≤40%).

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported for both arms.

| **Serious adverse events** | 10 mg Empagliflozin | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 155 (13.55%) | 27 / 156 (17.31%) | |
| number of deaths (all causes) | 3 | 3 | |
| number of deaths resulting from adverse events | 3 | 3 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertensive urgency | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 155 (1.29%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 6 / 155 (3.87%) | 12 / 156 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 12 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (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 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 155 (1.29%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dizziness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 155 (0.65%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Ear and labyrinth disorders** | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Gastrointestinal disorders** | | | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver injury | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| 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 | | | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Renal injury | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Parotitis | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (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 | 2 / 155 (1.29%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (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 | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval abscess | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 1 / 156 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 155 (0.65%) | 0 / 156 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | 10 mg Empagliflozin | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 155 (0.00%) | 0 / 156 (0.00%) | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 May 2018 | The following changes were introduced by the first global protocol amendment:<br><br>• Clarification of the inclusion criteria regarding medical therapy for heart failure (HF) (it was allowed to include patients who were not treated according to local guidelines, in such cases the investigator had to document the reasons)<br>• Clarification of the exclusion criteria regarding exclusion of patients randomised in another empagliflozin HF trial (a patient could be a screen failure in another trial and<br>then be considered for inclusion into this trial)<br><br>• Flowchart: Recommendation that NT-proBNP and safety laboratory measures should<br>be done first at the Screening Visit and then other procedures could be done on a later<br>day<br>• Updates to reflect the final version of the CHQ-SAS questionnaire<br>• Clarification that re-testing for eligibility criteria could be done only once<br>• Clarification that screening data of patients who failed screening can be used in the<br>parallel trial 1245-0167<br>• Clarification of the exclusion criteria regarding major surgery (patients were not<br>eligible for the trial if they had major surgery scheduled during the duration of the trial)<br>• Update of requirements for emergency situations<br>• Change of instructions for physical examinations<br>• Editorial changes and clarifications regarding the conduct of the 6MWT (described in<br>detail in the Appendix of the CTP) |
| 20 July 2018 | The following changes were introduced by the second global protocol amendment:<br>• Change of the inclusion criteria regarding the NT-proBNP level at baseline (influence<br>of atrial fibrillation was taken into account, new levels were >450 pg/ml for patients<br>without atrial fibrillation and >600 pg/ml for patients with atrial fibrillation)<br>• Flow chart: Clarification that at the time of the NT-proBNP measurement, the<br>baseline rhythm of the patient (e.g. sinus rhythm, atrial fibrillation) had to be determined (i.e. by ECG) in order to assess eligibility (see NT-proBNP cut-offs above) |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported