



Clinical trial results:

A multicentre, randomised, double-blind, 90-day superiority trial to evaluate the effect on clinical benefit, safety and tolerability of once daily oral EMPagliflozin 10 mg compared to placebo, initiated in patients hospitalised for acUte heart faiLure (de novo or decompensated chronic HF) who have been StabilisEd (EMPULSE)

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2019-002946-19 |
| Trial protocol | SE NL BE DE DK ES HU PL IT |
| Global end of trial date | 02 June 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 26 May 2022 |
| First version publication date | 26 May 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 1245-0204 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04157751 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Boehringer Ingelheim, Call Centre |
| Sponsor organisation address | Binger Straße 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 018002430127, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim, Boehringer Ingelheim, Call Centre, 001 18002430127, clintrriage.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 | 20 July 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 May 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess whether in-hospital administration of empagliflozin results in improvement in heart failure-related outcomes (clinical benefit including death, heart failure events (HFE), and the burden of symptoms as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score) in patients hospitalised for acute heart failure (de novo or decompensated chronic heart failure) and after initial stabilisation. Secondary objectives were to further assess whether it is safe to start empagliflozin in patients admitted to hospital in this setting.

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.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 04 June 2020 |
| 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 | Japan: 32 |
| Country: Number of subjects enrolled | China: 28 |
| Country: Number of subjects enrolled | Germany: 62 |
| Country: Number of subjects enrolled | Poland: 62 |
| Country: Number of subjects enrolled | Spain: 47 |
| Country: Number of subjects enrolled | Netherlands: 49 |
| Country: Number of subjects enrolled | Denmark: 35 |
| Country: Number of subjects enrolled | Italy: 29 |
| Country: Number of subjects enrolled | Czechia: 19 |
| Country: Number of subjects enrolled | Hungary: 20 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Norway: 12 |
| Country: Number of subjects enrolled | Sweden: 10 |
| Country: Number of subjects enrolled | United States: 134 |
| Country: Number of subjects enrolled | Canada: 12 |
| Worldwide total number of subjects | 566 |
| EEA total number of subjects | 360 |

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) | 184 |
| From 65 to 84 years | 334 |
| 85 years and over | 48 |

Subject disposition

Recruitment

Recruitment details:

A multicentre, randomised, double-blind trial to assess whether in-hospital administration of empagliflozin results in improvement in heart failure-related outcomes compared to placebo in patients with acute heart failure.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

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, Data analyst, Assessor |

Blinding implementation details:

Patients, investigators, central reviewers, 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 access to the randomisation code was restricted until its release for analysis.

The data monitoring committee (DMC) was provided with unblinded data to allow them to review efficacy and safety and to fulfil their tasks as outlined in the DMC charter.

Arms

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

Arm description:

1 film-coated tablet of placebo matching 10 mg empagliflozin was administered orally once daily in patients with acute heart failure.

| | |
|--|--------------------|
| 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 10 mg empagliflozin was administered orally once daily in patients with acute heart failure.

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

Arm description:

1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily in patients with acute heart failure.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Empagliflozin |
| 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 10 milligram (mg) of empagliflozin was administered orally once daily in patients

with acute heart failure.

| Number of subjects in period 1^[1] | Placebo | 10 mg Empagliflozin |
|---|---------|---------------------|
| Started | 265 | 265 |
| Treated | 264 | 260 |
| Completed | 202 | 208 |
| Not completed | 63 | 57 |
| Other reason not stated above | 10 | 10 |
| Consent withdrawn by subject | 12 | 17 |
| Adverse event, non-fatal | 34 | 23 |
| Lost to follow-up | 6 | 2 |
| Not treated | 1 | 5 |

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: Worldwide 566 patients were enrolled, whereof 530 patients were actually included in the study.

Baseline characteristics

Reporting groups

| | |
|---|---------------------|
| Reporting group title | Placebo |
| Reporting group description: 1 film-coated tablet of placebo matching 10 mg empagliflozin was administered orally once daily in patients with acute heart failure. | |
| Reporting group title | 10 mg Empagliflozin |
| Reporting group description: 1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily in patients with acute heart failure. | |

| Reporting group values | Placebo | 10 mg Empagliflozin | Total |
|---|---------|---------------------|-------|
| Number of subjects | 265 | 265 | 530 |
| Age categorical | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| 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) | 91 | 81 | 172 |
| From 65-84 years | 144 | 168 | 312 |
| 85 years and over | 30 | 16 | 46 |
| Age Continuous | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: years | | | |
| arithmetic mean | 68.1 | 68.9 | |
| standard deviation | ± 13.8 | ± 12.6 | - |
| Sex: Female, Male | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: Participants | | | |
| Female | 93 | 86 | 179 |
| Male | 172 | 179 | 351 |
| Race (NIH/OMB) | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 0 | 2 |
| Asian | 25 | 32 | 57 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 33 | 21 | 54 |
| White | 202 | 211 | 413 |
| More than one race | 2 | 1 | 3 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Ethnicity (NIH/OMB) | | | |

| | | | |
|--|---------|---------|-----|
| Randomised Set (RS), including all randomised patients. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 9 | 6 | 15 |
| Not Hispanic or Latino | 256 | 259 | 515 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Kansas City cardiomyopathy questionnaire-Total symptom score (KCCQ-TSS) | | | |
| The Kansas City Cardiomyopathy Questionnaire is a self-administered questionnaire that includes 23 items that map to 7 domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life and self-efficacy. The symptom frequency and symptom burden domains are merged into a total symptom score. Scores are represented on a 0-to-100-point scale, where a higher score reflects a better health status. KCCQ-TSS at baseline is reported. Only participants in the randomised set and with non-missing data are included. | | | |
| Units: Score on a scale | | | |
| arithmetic mean | 41.91 | 39.71 | |
| standard deviation | ± 23.98 | ± 24.06 | - |

Subject analysis sets

| | |
|----------------------------|---------------|
| Subject analysis set title | Overall Group |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Overall group contains both empagliflozin and placebo group. Empagliflozin group: 1 film-coated tablet of 10 milligram (mg) empagliflozin was administered orally once daily in patients with acute heart failure.

Placebo group: 1 film-coated tablet of placebo matching 10 mg empagliflozin was administered orally once daily in patients with acute heart failure.

| | | | |
|---|---------------|--|--|
| Reporting group values | Overall Group | | |
| Number of subjects | 530 | | |
| Age categorical | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 172 | | |
| From 65-84 years | 312 | | |
| 85 years and over | 46 | | |
| Age Continuous | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: years | | | |
| arithmetic mean | 68.5 | | |
| standard deviation | ± 13.2 | | |
| Sex: Female, Male | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: Participants | | | |
| Female | 179 | | |
| Male | 351 | | |

| | | | |
|--|---------|--|--|
| Race (NIH/OMB) | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | | |
| Asian | 57 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 54 | | |
| White | 413 | | |
| More than one race | 3 | | |
| Unknown or Not Reported | 1 | | |
| Ethnicity (NIH/OMB) | | | |
| Randomised Set (RS), including all randomised patients. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 15 | | |
| Not Hispanic or Latino | 515 | | |
| Unknown or Not Reported | 0 | | |
| Kansas City cardiomyopathy questionnaire-Total symptom score (KCCQ-TSS) | | | |
| The Kansas City Cardiomyopathy Questionnaire is a self-administered questionnaire that includes 23 items that map to 7 domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life and self-efficacy. The symptom frequency and symptom burden domains are merged into a total symptom score. Scores are represented on a 0-to-100-point scale, where a higher score reflects a better health status. KCCQ-TSS at baseline is reported. Only participants in the randomised set and with non-missing data are included. | | | |
| Units: Score on a scale | | | |
| arithmetic mean | 40.81 | | |
| standard deviation | ± 24.02 | | |

End points

End points reporting groups

| | |
|---|---------------------|
| Reporting group title | Placebo |
| Reporting group description: 1 film-coated tablet of placebo matching 10 mg empagliflozin was administered orally once daily in patients with acute heart failure. | |
| Reporting group title | 10 mg Empagliflozin |
| Reporting group description: 1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily in patients with acute heart failure. | |
| Subject analysis set title | Overall Group |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Overall group contains both empagliflozin and placebo group. Empagliflozin group: 1 film-coated tablet of 10 milligram (mg) empagliflozin was administered orally once daily in patients with acute heart failure. Placebo group: 1 film-coated tablet of placebo matching 10 mg empagliflozin was administered orally once daily in patients with acute heart failure. | |

Primary: Clinical benefit, a composite of death, number of heart failure events (HFEs), time to the first HFE and ≥ 5 -point difference in change from baseline in KCCQ-TSS after 90 days of treatment

| | |
|---|--|
| End point title | Clinical benefit, a composite of death, number of heart failure events (HFEs), time to the first HFE and ≥ 5 -point difference in change from baseline in KCCQ-TSS after 90 days of treatment |
| End point description: Win ratio (WR) is a method for providing an estimate of the treatment effect when composite endpoints are analyzed as the analysis accounts for clinical significance of outcomes of interest in a hierarchical manner. Pairwise comparisons of each patient in the empagliflozin (empa) group with each patient in the placebo (pbo) group were performed within strata. The hierarchical sequence was stopped once an advantage for a patient was shown. Stratified win ratio was used, calculated as total number of wins in the empa group across all strata divided by total number of losses. Weights were applied analogous to a Mantel-Haenszel approach. $WR\ estimate = \frac{((a)+(c)+(e)+(g))}{((b)+(d)+(f)+(h))}$; (a) death in pbo first; (b) death in empa first; (c) HFEs in pbo more frequently; (d) HFEs in empa more frequently; (e) HFEs in pbo first; (f) HFEs in empa first; (g) KCCQ-TSS change lower in pbo; (h) KCCQ-TSS change lower in empa; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire-Total Symptom Score | |
| End point type | Primary |
| End point timeframe: Up to 90 days. For KCCQ-TSS: at baseline and at day 90. | |

| End point values | Placebo | 10 mg Empagliflozin | Overall Group | |
|----------------------------------|-------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 265 ^[1] | 265 ^[2] | 530 ^[3] | |
| Units: Ratio | | | | |
| number (confidence interval 95%) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | 1.36 (1.09 to 1.68) | |

Notes:

[1] - (-)99999 stands for non-applicable value. Result is reported for Overall Group.

[2] - (-)99999 stands for non-applicable value. Result is reported for Overall Group.

[3] - Randomised Set (RS), including all randomised patients.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| H0: There is no difference between the effect of placebo and the effect of empagliflozin or the effect of placebo is greater. One-sided test at significance level of 0.025 | |
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0027 ^[4] |
| Method | Asymptotic normal U statistics approach |

Notes:

[4] - p-value for WR <= 1.0

Secondary: Number of participants with improvement of at least 10 points in KCCQ-TSS after 90 days of treatment

| | |
|-----------------|--|
| End point title | Number of participants with improvement of at least 10 points in KCCQ-TSS after 90 days of treatment |
|-----------------|--|

End point description:

Number of participants with improvement of at least 10 points in Kansas City Cardiomyopathy Questionnaire - Total Symptom Score (KCCQ-TSS) from baseline after 90 days of treatment.

The Kansas City Cardiomyopathy Questionnaire is a self-administered questionnaire that includes 23 items that map to 7 domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life and self-efficacy. The symptom frequency and symptom burden domains are merged into the total symptom score. Scores are represented on a 0-to-100-point scale, where a higher score reflects a better health status.

Randomised Set (RS), including all randomised patients.

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

End point timeframe:

At baseline and at day 90.

| End point values | Placebo | 10 mg Empagliflozin | | |
|-----------------------------|-----------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 265 | 265 | | |
| Units: Participants | 202 | 220 | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Logistic regression including terms for baseline KCCQ-TSS, treatment and heart failure status. 95% wald confidence intervals. | |
| Comparison groups | 10 mg Empagliflozin v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.097 ^[5] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.522 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.927 |
| upper limit | 2.501 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.386 |

Notes:

[5] - p-value for OR=1.0 (two-sided).

Secondary: Change from baseline in KCCQ-TSS after 90 days of treatment

| | |
|-----------------|---|
| End point title | Change from baseline in KCCQ-TSS after 90 days of treatment |
|-----------------|---|

End point description:

Change from baseline in Kansas City Cardiomyopathy Questionnaire - Total Symptom Score (KCCQ-TSS).

The Kansas City Cardiomyopathy Questionnaire is a self-administered questionnaire that includes 23 items that map to 7 domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life and self-efficacy. The symptom frequency and symptom burden domains are merged into the total symptom score. The score is represented on a 0-to-100-point scale, where a higher score reflects a better health status.

Change from baseline in KCCQ-TSS at day 90 was modeled using a MMRM with visit (day 15 and day 30) as repeated measures, mean (standard error) after 90 days of treatment is reported.

Patients in the randomised set (RS) and with non-missing data for this endpoint. Observed case including data after treatment discontinuation (OC-AD).

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

End point timeframe:

At baseline, at day 15, 30 and at day 90.

| End point values | Placebo | 10 mg Empagliflozin | | |
|-------------------------------------|-----------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 221 | 230 | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | 31.73 (± 1.49) | 36.19 (± 1.48) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|----------------------------|------------------------|

Statistical analysis description:

Restricted maximum likelihood estimation based on a mixed-effect model for repeated measures

(MMRM) analysis to obtain adjusted means for the treatment effects. This model included discrete fixed effects for treatment group, and heart failure status at each visit and continuous fixed effects for baseline value at each visit. Missing data caused by patient withdrawal or other reasons were handled implicitly by the MMRM approach. Unstructured covariance structure was used.

| | |
|---|-------------------------------|
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 451 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0347 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | Difference of adjusted mean |
| Point estimate | 4.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 8.59 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.1 |

Notes:

[6] - p-value for difference = 0 (two-sided)

Secondary: Change from baseline in log-transformed N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) Area under the curve (AUC) over 30 days of treatment

| | |
|-----------------|--|
| End point title | Change from baseline in log-transformed N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) Area under the curve (AUC) over 30 days of treatment |
|-----------------|--|

End point description:

Change from baseline in log-transformed N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) Area under the curve (AUC) over 30 days of treatment is reported.
Least Squares Mean is actually geometric Least Squares Mean

Patients included the randomised set (RS), and with non-missing data for this endpoint.

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

End point timeframe:

From baseline and to day 30.

| End point values | Placebo | 10 mg Empagliflozin | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 256 | 255 | | |
| Units: Picogram/milliliter * days | | | | |
| least squares mean (confidence interval 95%) | 26.77 (25.15 to 28.48) | 24.07 (22.61 to 25.62) | | |

Statistical analyses

| | |
|--|-------------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: | |
| Area under the curve (AUC) of change from baseline in log-transformed NT-proBNP level over 30 days of treatment was analysed by an analysis of covariance (ANCOVA). NT-proBNP level is regarded as log-normally distributed, therefore values were log-transformed prior to analysis. The linear trapezoidal rule was used to calculate the AUC after the log-transformation had been applied to each value. | |
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0176 ^[7] |
| Method | ANCOVA |
| Parameter estimate | Adjusted geometric mean ratio |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 0.98 |

Notes:

[7] - Two-sided

Secondary: Percentage of days alive and out of hospital (DAOH) from study drug initiation until 30 days after initial hospital discharge

| | |
|-----------------|---|
| End point title | Percentage of days alive and out of hospital (DAOH) from study drug initiation until 30 days after initial hospital discharge |
|-----------------|---|

End point description:

The follow-up time for DAOH analyses was defined as 30 days after initial hospital discharge, or time between initial hospital discharge and date of censoring for non-fatal events except for patients who died within the first 30 days, where 30 days was considered as the DAOH follow-up time.

DAOH for each patient was calculated as follow-up time subtracted by the number of days in hospital during the 30 days after initial hospital discharge as well as the number of days being dead within the 30 days. Percentage DAOH was defined as DAOH divided by the DAOH follow-up time of each patient multiplied by 100.

Patients included the treated set (TS), and with non-missing data for this endpoint. TS includes all patients treated with at least one dose of trial medication.

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

End point timeframe:

Up to 30 days after initial hospital discharge.

| End point values | Placebo | 10 mg Empagliflozin | | |
|--------------------------------------|-----------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 264 | 258 | | |
| Units: DAOH in percentage (%) | | | | |
| arithmetic mean (standard deviation) | 80.90 (± 21.25) | 81.37 (± 18.62) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of days alive and out of hospital (DAOH) from study drug initiation until 90 days after randomisation

| | |
|-----------------|--|
| End point title | Percentage of days alive and out of hospital (DAOH) from study drug initiation until 90 days after randomisation |
|-----------------|--|

End point description:

The follow-up time for DAOH analyses was defined as 90 days after randomisation, or time between randomisation and date of censoring for non-fatal events except for patients who died within the first 90 days, where 90 days was considered as the DAOH follow-up time. DAOH for each patient was calculated as follow-up time subtracted by the number of days in hospital during the 90 days after randomisation as well as the number of days being dead within the first 90 days. Percentage DAOH was defined as DAOH divided by the DAOH follow-up time of each patient multiplied by 100.

Patients in the treated set (TS) and with non-missing data for this endpoint.

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

End point timeframe:

Up to 90 days after randomisation.

| End point values | Placebo | 10 mg Empagliflozin | | |
|--------------------------------------|--------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 260 | 257 | | |
| Units: DAOH in percentage (%) | | | | |
| arithmetic mean (standard deviation) | 85.79 (± 22.76) | 87.55 (± 19.54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of first occurrence of cardiovascular (CV) death or heart failure event (HFE) until end of trial visit

| | |
|-----------------|---|
| End point title | Incidence rate of first occurrence of cardiovascular (CV) death or heart failure event (HFE) until end of trial visit |
|-----------------|---|

End point description:

Incidence rate of first occurrence of CV death or HFE until end of trial visit per 100 patient-year (pt-yrs) at risk is reported. Incidence rate per 100 pt-yrs = 100* number of patients with event / time at risk [years].

Randomised Set (RS), including all randomised patients.

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

End point timeframe:

Up to 127 days.

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|-------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 265 | 265 | | |
| Units: Patients with events / 100pt-yrs at risk | | | | |
| number (confidence interval 95%) | 78.81 (58.11 to 102.62) | 55.01 (38.10 to 74.99) | | |

Statistical analyses

| | |
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| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: Comparison vs. Placebo. | |
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1241 ^[8] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 1.1 |

Notes:

[8] - p-value for HR=1.0 (two sided)

Secondary: Number of participants with hospitalization for heart failure (HHF) until 30 days after initial hospital discharge

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| End point title | Number of participants with hospitalization for heart failure (HHF) until 30 days after initial hospital discharge |
| End point description: Number of participants with hospitalization for heart failure (HHF) until 30 days after initial hospital discharge. | |
| Randomised Set (RS), including all randomised patients. | |
| End point type | Secondary |
| End point timeframe: Up to 30 days after initial hospital discharge. | |

| End point values | Placebo | 10 mg Empagliflozin | | |
|-----------------------------|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 265 | 265 | | |
| Units: Participants | 12 | 14 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Composite renal endpoint: Number of participants with chronic dialysis, renal transplant, sustained reduction in eGFR(CKD-EPI)cr

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| End point title | Composite renal endpoint: Number of participants with chronic dialysis, renal transplant, sustained reduction in eGFR(CKD-EPI)cr |
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End point description:

The occurrence of the composite renal endpoint:

- chronic dialysis (with a frequency of twice per week or more for at least 90 days), or
 - renal transplant, or
 - sustained reduction in Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement (eGFR (CKD-EPI)cr) from baseline of $\geq 40\%$, or
 - sustained eGFR [mL/min/1.73 m²] < 15 and baseline value ≥ 30 , or
 - sustained eGFR < 10 and baseline value < 30 ;
- is reported by number of participants with component events. (These events may have occurred after the endpoint was already met. Combinations may not have occurred on the same day).

Sustained was determined by 2 or more consecutive post-baseline central laboratory measurements separated by at least 30 days.

Randomised Set (RS), including all randomised patients.

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

End point timeframe:

Up to 90 days.

| End point values | Placebo | 10 mg Empagliflozin | | |
|-----------------------------|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 265 | 265 | | |
| Units: Participants | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Weight change per mean daily loop diuretic dose after 15 days of treatment

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| End point title | Weight change per mean daily loop diuretic dose after 15 days of treatment |
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End point description:

Diuretic effect as assessed by weight change per mean daily loop diuretic dose after 15 days of treatment.

Diuretic dose = 40 mg intravenous furosemide or 80 mg oral furosemide.

Abbreviation:

Kg: Kilogram

Patients in the randomised set (RS) and with non-missing data for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
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End point timeframe:

At baseline and at day 15.

| End point values | Placebo | 10 mg Empagliflozin | | |
|--------------------------------------|--------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 224 | 212 | | |
| Units: Kg per loop diuretic dose | | | | |
| arithmetic mean (standard deviation) | -2.43 (± 23.46) | -4.45 (± 16.65) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Weight change per mean daily loop diuretic dose after 30 days of treatment

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| End point title | Weight change per mean daily loop diuretic dose after 30 days of treatment |
|-----------------|--|

End point description:

Diuretic effect as assessed by weight change per mean daily loop diuretic dose after 30 days of treatment.

Diuretic dose = 40 mg intravenous furosemide or 80 mg oral furosemide

Abbreviation:

Kg: Kilogram

Patients in the randomised set (RS) and with non-missing data for this endpoint.

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

End point timeframe:

At baseline and at day 30.

| End point values | Placebo | 10 mg Empagliflozin | | |
|--------------------------------------|--------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216 | 219 | | |
| Units: Kg per loop diuretic dose | | | | |
| arithmetic mean (standard deviation) | -2.69 (± 21.74) | -6.91 (± 25.34) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

[All-cause Mortality]: From first study drug intake until end of follow-up, up to 202 days.

[Serious and Other Adverse Event]: From first study drug intake until 7 days after last intake of study medication, up to 127 days.

Adverse event reporting additional description:

[All-cause Mortality]: Randomised Set (RS) including all randomised patients. The actual number of subjects at risk for all-cause death is 265 for empagliflozin and placebo arm. [Serious and Other Adverse Events]: Treated Set (TS), consisting of all patients treated with at least once dose of trial medication.

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| Assessment type | Systematic |
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Dictionary used

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|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

Reporting groups

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

Reporting group description:

1 film-coated tablet of 10 milligram (mg) of empagliflozin was administered orally once daily in patients with acute heart failure.

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

Reporting group description:

1 film-coated tablet of placebo matching 10 mg empagliflozin was administered orally once daily in patients with acute heart failure.

| Serious adverse events | 10 mg Empagliflozin | Placebo | |
|---|---------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 84 / 260 (32.31%) | 115 / 264 (43.56%) | |
| number of deaths (all causes) | 11 | 22 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic neoplasm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 5 / 264 (1.89%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypertensive emergency | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| 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 | 2 / 260 (0.77%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular stent stenosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| 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 pulmonary oedema | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| 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 | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary hypertension | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dislocation of vertebra | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye injury | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Fall | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament sprain | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Gastrointestinal arteriovenous malformation | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|-------------------|--|
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 5 / 264 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Bradycardia | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 25 / 260 (9.62%) | 37 / 264 (14.02%) | |
| occurrences causally related to treatment / all | 1 / 32 | 0 / 43 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 11 / 264 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (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 | 2 / 260 (0.77%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic left ventricular failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 260 (0.38%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary ostial stenosis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Silent myocardial infarction | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (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 / 260 (0.00%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| 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 | 8 / 260 (3.08%) | 7 / 264 (2.65%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery dissection | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monoplegia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cauda equina syndrome | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraplegia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| 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 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic encephalopathy | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (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 | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (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 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric arteriosclerosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Congestive hepatopathy | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| 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 ulcer | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 10 / 260 (3.85%) | 19 / 264 (7.20%) | |
| occurrences causally related to treatment / all | 5 / 12 | 5 / 19 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephropathy | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 260 (0.77%) | 4 / 264 (1.52%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal artery stenosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (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 | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 3 / 264 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis A | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 4 / 264 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 264 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 264 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gout | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 264 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| 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 | 20 / 260 (7.69%) | 19 / 264 (7.20%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 20 / 260 (7.69%) | 19 / 264 (7.20%) | |
| occurrences (all) | 22 | 19 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 04 June 2020 | <ul style="list-style-type: none">- Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score (KCCQ-CSS) was exchanged by Kansas City Cardiomyopathy Questionnaire – Total Summary Score (KCCQ-TSS) in trial objectives and all respective endpoints (primary, secondary, and further endpoints). Rationale: The TSS was found to be more responsive to the patient's symptoms based on results from EMPERIAL-reduced and other Sodium Glucose Co-Transporter 2 (SGLT2)-inhibitor trials (with dapagliflozin).- Statistical methodology for primary endpoint was changed from 'net benefit' to 'win ratio'. Rationale: The win ratio has gained attention in the scientific community based on recent publications and public scientific discussions. Compared with the 'net benefit' approach, the result arising from the 'win ratio' will likely be better understood by regulatory authorities and by the scientific community. The overall statistical power for the primary endpoint remained very similar (e.g. 87.2% with the net benefit and 87.4% with the win ratio using the same assumptions). Global Amendment continues. |
| 04 June 2020 | <p>Patient global impression of severity of heart failure (HF) symptoms (PGI-S) was added as a patient reported outcome measure and the endpoint 'change from baseline in PGI-S of HF symptoms after 90 days of treatment' was added. Rationale: The PGI-S of HF symptoms can be used as an anchor to identify the clinically meaningful within-patient change in KCCQ (a component of the primary endpoint). The collection of PGI-S data was to facilitate addressing the question of clinical meaningfulness.</p> <ul style="list-style-type: none">- Risk evaluation in relation with COVID-19 was added. Rationale: Measures taken during the COVID-19 pandemic.- Contingency measures have been introduced to ensure patient safety and appropriate trial continuation based on a thorough benefit risk assessment. Flexibility for trial visits was introduced (allow in exceptional cases visits to be done as home/remote visits; allow for Investigational medicinal product (IMP) shipment from site to patient. Rationale: Measures taken during the COVID-19 pandemic. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported