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 decompensatied 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, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Boehringer Ingelheim, Call Centre, 001 18002430127, 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	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= [((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

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

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

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 ≥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.

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

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

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

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

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

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

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 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	

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	

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			

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	- 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	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. - 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