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

Summary

EudraCT number	2017-004072-59
Trial protocol	ES GR PT PL SE NO IT
Global end of trial date	09 October 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	1245-0167

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03448406
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Straße 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 55216 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 55216 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	11 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2019
Global end of trial reached?	Yes
Global end of trial date	09 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the effect of empagliflozin 10 mg vs. placebo on exercise ability using the 6-minute walk test (6MWT) in patients with chronic heart failure (CHF) with preserved left ventricular ejection fraction (LVEF >40%).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Greece: 28
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Poland: 120
Country: Number of subjects enrolled	Portugal: 42
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	United States: 318
Worldwide total number of subjects	719
EEA total number of subjects	361

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	176
From 65 to 84 years	508
85 years and over	35

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

1 film-coated tablet of Placebo matching Empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with preserved ejection fraction (LVEF > 40%).

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

Dosage and administration details:

1 film-coated tablet of Placebo matching empagliflozin was admininstered orally once daily for 12 weeks in subjects with chronic heart failure (CHF) with preserved ejection fraction (LVEF > 40%).

Arm title	10 mg Empagliflozin

Arm description:

1 film-coated tablet of 10 milligram (mg) of Empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with with preserved ejection fraction (LVEF > 40%).

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

Dosage and administration details:

1 film-coated tablet of 10 milligram (m) of Empagliflozin was administered orally once daily for 12 weeks in subjects with chronic heart failure (CHF) with perserved ejection fraction (LVEF > 40%).

Number of subjects in period 1[1]	Placebo	10 mg Empagliflozin
Started	158	157
Completed	147	144
Not completed	11	13
Noncompliance of scheduled visits	1	2
Protocol deviation	1	-
Adverse event, non-fatal	8	9
Consent withdrawn by subject	1	2

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: 719 subjects were enrolled worldwide and thereof 315 were entered in the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
1 film-coated tablet of Placebo matching Empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with preserved ejection fraction (LVEF > 40%).	
Reporting group title	10 mg Empagliflozin
Reporting group description:	
1 film-coated tablet of 10 milligram (mg) of Empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with with preserved ejection fraction (LVEF > 40%).	

Reporting group values	Placebo	10 mg Empagliflozin	Total
Number of subjects	158	157	315
Age categorical			
Randomised Set: All randomised subjects, regardless of whether treated or not.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	25	45
From 65-84 years	123	124	247
85 years and over	15	8	23
Age Continuous			
Randomised Set: All randomised subjects, regardless whether treated or not.			
Units: years			
arithmetic mean	73.9	73.0	
standard deviation	± 8.6	± 9.0	-
Sex: Female, Male			
Randomised Set: All randomised subjects, regardless of whether treated or not.			
Units: Participants			
Female	66	70	136
Male	92	87	179
Race (NIH/OMB)			
Randomised Set: All randomised subjects, regardless of whether treated or not.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	3	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	19	13	32
White	135	140	275
More than one race	2	0	2
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	19	18	37
Not Hispanic or Latino	139	138	277
Unknown or Not Reported	0	1	1
Exercise capacity as measured by the 6-Minutes-Walking-Test (6MWT) distance at baseline			
6 Minute Walking test measures the distance walked in 6 minutes in standardised conditions at baseline. Randomised Set: All randomised subjects, regardless of whether treated or not.			
Units: Meter			
median	299.5	297.0	
inter-quartile range (Q1-Q3)	245.0 to 331.0	246.0 to 326.0	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
1 film-coated tablet of Placebo matching Empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with preserved ejection fraction (LVEF > 40%).	
Reporting group title	10 mg Empagliflozin
Reporting group description:	
1 film-coated tablet of 10 milligram (mg) of Empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with with preserved ejection fraction (LVEF > 40%).	

Primary: Change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions (6MWTD)

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

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158[1]	157[2]		
Units: Meter (m)				
median (inter-quartile range (Q1-Q3))	5.0 (-20.0 to 33.0)	10.0 (-10.0 to 32.0)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Superiority of Empagliflozin vs. Placebo
Statistical analysis description:	
H0: There is no difference between the effect of Placebo and the effect of empagliflozin.	
Comparison groups	10 mg Empagliflozin v Placebo
Number of subjects included in analysis	315

Analysis specification	Pre-specified
Analysis type	
P-value	= 0.366
Method	Wilcoxon rank test, normal approximation
Parameter estimate	Median difference (HL-estimate)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	13

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

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

End point description:

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

End point type	Secondary

End point timeframe:

At baseline and at Week 12

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158[3]	157[4]		
Units: Score on a scale				
median (inter-quartile range (Q1-Q3))	2.08 (-6.25 to 20.83)	4.17 (-3.13 to 16.67)		

Notes:

[3] - Randomised Set (RS)

[4] - Randomised Set (RS)

Statistical analyses

Statistical analysis title	Superiority of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	315

Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2783
Method	Wilcoxon rank test, normal approximation
Parameter estimate	Median difference (HL-estimate)
Point estimate	2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	6.25

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

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

End point description:

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

End point type	Secondary

End point timeframe:

At baseline and at Week 12

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158[5]	156[6]		
Units: Score on a scale				
median (inter-quartile range (Q1-Q3))	0.20 (-0.40 to 1.00)	0.10 (-0.40 to 1.00)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Superiority of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	314
Analysis specification	Pre-specified

Analysis type	
P-value	= 0.5512
Method	Wilcoxon rank test, normal approximation
Parameter estimate	Median difference (HL-estimate)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.2

Secondary: Change from baseline to week 6 in exercise capacity as measured by the distance walked in 6 minutes

End point title	Change from baseline to week 6 in exercise capacity as measured by the distance walked in 6 minutes

End point description:

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

End point type	Secondary

End point timeframe:

At baseline and at Week 6

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158[7]	157[8]		
Units: Meter (m)				
median (inter-quartile range (Q1-Q3))	1.0 (-17.0 to 21.0)	7.0 (-14.0 to 23.0)		

Notes:

[7] - RS

[8] - RS

Statistical analyses

Statistical analysis title	Superiority of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3657
Method	Wilcoxon rank test, normal approximation

Parameter estimate	Median Difference (HL-estimate)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	11

Secondary: Change from baseline in Clinical Congestion Score at week 12

End point title	Change from baseline in Clinical Congestion Score at week 12

End point description:

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

End point type	Secondary

End point timeframe:

At baseline and at Week 12

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[9]	156[10]		
Units: Score on scale				
arithmetic mean (standard deviation)	-0.28 (± 0.08)	-0.36 (± 0.08)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Effect of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.444
Method	Mixed Model Repeated Measure (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	-0.09
Confidence interval	

level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.14
Variability estimate	Standard deviation
Dispersion value	0.11

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

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

End point description:

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

End point type	Secondary

End point timeframe:

At baseline and at Week 12

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154[11]	153[12]		
Units: Participants				
4 categories improvement	1	0		
3 categories improvement	2	1		
2 categories improvement	11	8		
1 category improvement	46	42		
No change	70	79		
1 category deterioration	17	16		
2 categories deterioration	6	6		
3 categories deterioration	0	1		
4 categories deterioration	1	0		

Notes:

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

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

Statistical analyses

Statistical analysis title	Effect of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	307

Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3924
Method	Cochran-Mantel-Haenszel test

Secondary: Change from baseline in Patient Global Impression of Severity (PGI-S) of Dyspnea Severity at week 12

End point title	Change from baseline in Patient Global Impression of Severity (PGI-S) of Dyspnea Severity at week 12

End point description:

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

End point type	Secondary

End point timeframe:

At baseline and at Week 12

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154[13]	153[14]		
Units: Participants				
4 categories improvement	1	0		
3 categories improvement	4	1		
2 categories improvement	8	13		
1 category improvement	45	48		
No change	70	70		
1 category deterioration	18	20		
2 categories deterioration	7	1		
3 categories deterioration	1	0		
4 categories deterioration	0	0		

Notes:

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

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

Statistical analyses

Statistical analysis title	Effect of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4435

Method	Cochran-Mantel-Haenszel test

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154[15]	153[16]		
Units: Participants				
Very much worse	1	0		
Much worse	0	3		
A little worse	11	7		
No change	62	55		
A little better	41	48		
Much better	31	35		
Very much better	8	5		

Notes:

[15] - Only subjects in the randomised set (RS) who have values at week 12 are included in the analysis.

[16] - Only subjects in the randomised set (RS) who have values at week 12 are included in the analysis.

Statistical analyses

Statistical analysis title	Effect of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5124
Method	Cochran−Mantel−Haenszel test

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154[17]	153[18]		
Units: Participants				
Very much worse	0	0		
Much worse	2	3		
A little worse	6	7		
No change	72	57		
A little better	32	45		
Much better	31	36		
Very much better	11	5		

Notes:

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

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

Statistical analyses

Statistical analysis title	Effect of Empagliflozin vs. Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5713
Method	Cochran−Mantel−Haenszel test

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

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

End point description:

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

have values at baseline and at week 12 were included in the analysis.

End point type	Secondary

End point timeframe:

Within 3 weeks prior to treatment start and at Week 12.

End point values	Placebo	10 mg Empagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[19]	156[20]		
Units: Ratio of adjusted geometric means				
number (confidence interval 95%)	1.04 (0.96 to 1.13)	0.99 (0.92 to 1.08)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Effect of Empagliflozin vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v 10 mg Empagliflozin
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4032
Method	Mixed model repeated Measure (MMRM)
Parameter estimate	Adjusted geometric mean ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.07

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From fist intake of study medication, until 7 days after the last intake of study medication, up to 92 days.

Adverse event reporting additional description:

Treated Set: All participants who were treated with at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	10 mg Empagliflozin

Reporting group description:

1 film-coated tablet of 10 milligram (mg) of Empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with with preserved ejection fraction (LVEF > 40%).

Reporting group title	Placebo

Reporting group description:

1 film-coated tablet of Placebo matching empagliflozin was administered orally once daily for 12 weeks in participants with chronic Heart Failure (CHF) with preserved ejection fraction (LVEF > 40%).

Notes:

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

Serious adverse events	10 mg Empagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 157 (12.74%)	29 / 158 (18.35%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to	0 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 157 (1.27%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	6 / 157 (3.82%)	13 / 158 (8.23%)	
occurrences causally related to treatment / all	0 / 6	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
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			
Aspiration			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
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 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (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 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (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	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to	0 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolic alkalosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (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			
Arthritis bacterial			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter duodenitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	10 mg Empagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 157 (0.00%)	0 / 158 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2018	The following changes were introduced by this protocol amendment: • Update of the affiliation of one of the CIs • Clarification of the inclusion criteria regarding prior use of diuretics (not mandatory for inclusion in the trial; if prescribed, dose had to appropriate and stable for 2 weeks prior to Visit 1) • Clarification of the exclusion criteria regarding exclusion of patients randomised in another empagliflozin HF trial (a patient could be a screen failure in another trial and then be considered for inclusion into this trial) • Flow chart: Recommendation that NT-proBNP and safety laboratory measures should be done first at the Screening Visit and then other procedures could be done on a later day • Updates to reflect the final version of the CHQ-SAS questionnaire • Clarification that re-testing for eligibility criteria could be done only once • Clarification that screening data of patients who failed screening can be used in the parallel trial 1245-0168 • Clarification of the exclusion criteria regarding major surgery (patients were not eligible for the trial if they had major surgery scheduled during the duration of the trial) • Update of requirements for emergency situations • Clarification that concomitant diseases were to be treated according to best standard of care and in accordance with prevailing guidelines • Correction of jugular venous distension categories • Change of instructions for physical examinations • Clarification when procedures at Visits 2 to 4 were to be done in relation to dosing • Editorial changes and clarifications regarding the conduct of the 6MWT (described in detail in the Appendix of the CTP)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported