Clinical trial results:
Empagliflozin in heart failure patients with reduced ejection fraction: A randomized clinical trial (Empire HF)

Summary

EudraCT number	2017-001341-27
Trial protocol	DK
Global end of trial date	20 December 2019

Results information

Result version number	v1 (current)
This version publication date	19 December 2020
First version publication date	19 December 2020
Summary attachment (see zip file)	Design paper (Design_Paper_Empire_HF.pdf)

Trial information

Trial identification

Sponsor protocol code	Empire-2017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03198585
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Morten Schou
Sponsor organisation address	Department of Cardiology, Herlev-Gentofte University Hospital, Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
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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	13 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2019
Global end of trial reached?	Yes
Global end of trial date	20 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of 3 months' treatment with Empagliflozin 10 mg a day on changes in plasma concentrations of NT-proBNP in stable, symptomatic HF patients with reduced left ventricular ejection fraction (LVEF).

Protection of trial subjects:

The safety of randomized patients was monitored continuously based on recordings of adverse and severe adverse events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2017
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	Denmark: 190
Worldwide total number of subjects	190
EEA total number of subjects	190

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)	100
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period June 29, 2017, to September 10, 2019. Recruited from heart failure clinics in Denmark.

Pre-assignment

Screening details:

No wash-out or run-in. In total, 697 were assessed for eligibility, 507 were excluded (n=317 not meeting inclusion criteria, n=139 declined to participate, n=51 due to other reasons).

Period 1

Period 1 title	Overall period (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

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg once daily	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Matching	

Number of subjects in period 1	Empagliflozin	Placebo
Started	95	95
Completed	95	94
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Empagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Empagliflozin	Placebo	Total
Number of subjects	95	95	190
Age categorical 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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	64	63	
inter-quartile range (Q1-Q3)	57 to 73	55 to 72	-
Gender categorical Units: Subjects			
Female	16	12	28
Male	79	83	162

End points

End points reporting groups	
Reporting group title	Empagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: NT-proBNP	
End point title	NT-proBNP
End point description:	
End point type	Primary
End point timeframe:	
Baseline to 90 days	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	92		
Units: Ratio of change				
median (inter-quartile range (Q1-Q3))	0.96 (0.69 to 1.24)	0.93 (0.77 to 1.21)		

Statistical analyses

Statistical analysis title	NT-proBNP
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.11

Secondary: Daily activity level	
End point title	Daily activity level
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 90 days	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	84		
Units: Difference of change				
arithmetic mean (standard deviation)	-54.6 (± 253.3)	-4.9 (± 198.3)		

Statistical analyses

Statistical analysis title	Daily activity level
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-88
upper limit	36

Secondary: Health-related quality of life (KCCQ)	
End point title	Health-related quality of life (KCCQ)
End point description:	
KCCQ overall summary score	
End point type	Secondary
End point timeframe:	
Baseline to 90 days	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	92		
Units: Difference of change				
arithmetic mean (standard deviation)	1.9 (± 12.3)	1.2 (± 9.4)		

Statistical analyses

Statistical analysis title	KCCQ
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	3.9

Secondary: Health-related quality of life (EQ-5D-5L)

End point title	Health-related quality of life (EQ-5D-5L)
End point description: EQ-5D-5L VAS	
End point type	Secondary
End point timeframe: Baseline to 90 days	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	92		
Units: Difference of change				
arithmetic mean (standard deviation)	2.4 (± 13.6)	3.6 (± 14.6)		

Statistical analyses

Statistical analysis title	EQ-5D-5L
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	2.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to 90 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	None
Dictionary version	1
Reporting groups	
Reporting group title	Empagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Empagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 95 (6.32%)	4 / 95 (4.21%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Heart failure hospitalization			
subjects affected / exposed	1 / 95 (1.05%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardioversion of atrial fibrillation or flutter			
subjects affected / exposed	3 / 95 (3.16%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 95 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 95 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Stroke			
subjects affected / exposed	1 / 95 (1.05%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 95 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 95 (1.05%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recurrent bladder cancer			
subjects affected / exposed	1 / 95 (1.05%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gout			
subjects affected / exposed	1 / 95 (1.05%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fracture			
subjects affected / exposed	0 / 95 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Empagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 95 (7.37%)	9 / 95 (9.47%)	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	3 / 95 (3.16%)	3 / 95 (3.16%)	
occurrences (all)	3	3	
Genital infection			
subjects affected / exposed	3 / 95 (3.16%)	5 / 95 (5.26%)	
occurrences (all)	3	5	
Endocrine disorders			
Hypoglycemia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 95 (1.05%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32798787