Clinical trial results:
Empagliflozin as a Modulator of Systemic Vascular Resistance and Cardiac Output in Patients with Type 2 Diabetes

Summary

EudraCT number	2016-000172-19
Trial protocol	DE
Global end of trial date	23 January 2019

Results information

Result version number	v1 (current)
This version publication date	30 October 2021
First version publication date	30 October 2021

Trial information

Trial identification

Sponsor protocol code	15-124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03132181
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	RWTH Aachen University for the Medical Faculty, represented by Center for Translational & Clinical Research Aachen (CTC-A)
Sponsor organisation address	Pauwelsstraße 30, Aachen, Germany, 52074
Public contact	Center for Translational & Clinical Research Aachen (CTC-A), RWTH Aachen University, +49 2418080092, ctc-a-sekretariat@ukaachen.de
Scientific contact	Center for Translational & Clinical Research Aachen (CTC-A), RWTH Aachen University, +49 2418080092, ctc-a-sekretariat@ukaachen.de

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	29 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2019
Global end of trial reached?	Yes
Global end of trial date	23 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Effect of empagliflozin 10 mg once daily on cardiac output in comparison to placebo after 1 day, 3 days and 12 weeks of treatment (measured with a noninvasive monitoring [ClearSight System]).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	27
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment and treatment of subjects was performed in one trial center. Overall 44 subjects were enrolled and randomized in the clinical trial in the timeframe from 02.05.2017 till 22.10.2018.

Pre-assignment

Screening details:

Overall 55 subjects were screened in one trial center. Of those 55 subjects screened, 44 subjects met the inclusion and exclusion criteria and were enrolled and randomized in the clinical trial.

Period 1

Period 1 title	Baseline visit
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin

Arm description:

Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.

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 tablets once daily administered orally

Arm title	Placebo

Arm description:

Subjects in the Placebo arm receive one tablet once daily for 3 months.

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:

One tablet daily administered orally

Number of subjects in period 1	Empagliflozin	Placebo
Started	22	22
Completed	22	22

Period 2

Period 2 title	Day 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin

Arm description:

Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.

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 tablets once daily administered orally

Arm title	Placebo

Arm description:

Subjects in the Placebo arm receive one tablet once daily for 3 months.

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:

One tablet daily administered orally

Number of subjects in period 2	Empagliflozin	Placebo
Started	22	22
Completed	22	22

Period 3

Period 3 title	Day 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin

Arm description:

Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.

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 tablets once daily administered orally

Arm title	Placebo

Arm description:

Subjects in the Placebo arm receive one tablet once daily for 3 months.

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:

One tablet daily administered orally

Number of subjects in period 3	Empagliflozin	Placebo
Started	22	22
Completed	21	22
Not completed	1	0
Adverse event, non-fatal	1	-

Period 4

Period 4 title	3 Months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin

Arm description:

Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.

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 tablets once daily administered orally

Arm title	Placebo

Arm description:

Subjects in the Placebo arm receive one tablet once daily for 3 months.

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:

One tablet daily administered orally

Number of subjects in period 4	Empagliflozin	Placebo
Started	21	22
Completed	20	22
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Empagliflozin
Reporting group description:	
Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects in the Placebo arm receive one tablet once daily for 3 months.	

Reporting group values	Empagliflozin	Placebo	Total
Number of subjects	22	22	44
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			
arithmetic mean	62.4	61.2	
standard deviation	± 5.4	± 7.9	-
Gender categorical			
Units: Subjects			
Female	5	4	9
Male	17	18	35
Type 2 diabetes - Insulin treated			
Units: Subjects			
yes	12	8	20
no	10	14	24
Type 2 diabetes - Metformin treatment			
Units: Subjects			
yes	14	18	32
no	8	4	12
Type 2 diabetes - DPP-4 inhibitor treatment			
Units: Subjects			
yes	8	6	14
no	14	16	30
Type 2 diabetes - other treatments			
Units: Subjects			
yes	3	1	4
no	19	21	40

History of CVD - coronary heart disease Units: Subjects			
yes	17	15	32
no	5	7	12
History of CVD - myocardial infarction Units: Subjects			
yes	6	10	16
no	16	12	28
History of CVD - CABG Units: Subjects			
yes	5	4	9
no	17	18	35
History of CVD - PCI Units: Subjects			
yes	11	12	23
no	11	10	21
History of CVD - Peripheral artery disease Units: Subjects			
yes	4	2	6
no	18	20	38
Chronic heart failure Units: Subjects			
yes	7	11	18
no	15	11	26
Medication - antiplatelets Units: Subjects			
yes	13	16	29
no	9	6	15
Medication - Oral anticoagulants Units: Subjects			
yes	6	5	11
no	16	17	33
Medication - Diuretics Units: Subjects			
yes	10	10	20
no	12	12	24
Medication - Statins Units: Subjects			
yes	17	15	32
no	5	7	12
Medication - Calcium channel blockers Units: Subjects			
yes	4	5	9
no	18	17	35
Medication - Beta blockers Units: Subjects			
yes	18	16	34
no	4	6	10
Medication - RAAS inhibitors Units: Subjects			

yes	16	20	36
no	6	2	8

Body mass index			
Units: kg/m²			
arithmetic mean	31.7	31.2	
standard deviation	± 5.2	± 4.0	-
Systolic blood pressure			
Units: mmHg			
arithmetic mean	136	136	
standard deviation	± 16	± 18	-
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	83	81	
standard deviation	± 14	± 14	-
Heart rate			
Units: bpm			
arithmetic mean	71	69	
standard deviation	± 12	± 15	-
Type 2 diabetes - glycated hemoglobin			
Units: percentage			
arithmetic mean	7.5	8.0	
standard deviation	± 0.8	± 1.2	-
Type 2 diabetes - diabetes duration			
Units: years			
median	10	9	
inter-quartile range (Q1-Q3)	3 to 13	6 to 18	-
eGFR			
Units: ml/min/1.73m²			
arithmetic mean	78	88	
standard deviation	± 20	± 16	-
Total cholesterol			
Units: mg/dl			
arithmetic mean	168	155	
standard deviation	± 39	± 39	-
LDL-C			
Units: mg/dl			
arithmetic mean	101	95	
standard deviation	± 35	± 38	-
HDL-C			
Units: mg/dl			
arithmetic mean	43	44	
standard deviation	± 9	± 9	-
Triglycerides			
Units: mg/dl			
arithmetic mean	247	156	
standard deviation	± 147	± 71	-

End points

End points reporting groups

Reporting group title	Empagliflozin
Reporting group description:	
Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects in the Placebo arm receive one tablet once daily for 3 months.	
Reporting group title	Empagliflozin
Reporting group description:	
Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects in the Placebo arm receive one tablet once daily for 3 months.	
Reporting group title	Empagliflozin
Reporting group description:	
Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects in the Placebo arm receive one tablet once daily for 3 months.	
Reporting group title	Empagliflozin
Reporting group description:	
Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects in the Placebo arm receive one tablet once daily for 3 months.	

Primary: Systemic vascular resistance index - Baseline

End point title	Systemic vascular resistance index - Baseline
End point description:	

End point type	Primary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	22		
Units: dyne*sec*cm^(-5)*m^(-2)				
arithmetic mean (standard deviation)	1841 (± 379)	1836 (± 361)		

Notes:

[1] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis SVRI - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.967
Method	Wald test

Primary: Systemic vascular resistance index - Day 1

End point title	Systemic vascular resistance index - Day 1
End point description:	
End point type	Primary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[2]	22		
Units: dyne*sec*cm^(-5)*m^(-2)				
arithmetic mean (standard deviation)	1864 (± 373)	1942 (± 355)		

Notes:

[2] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis SVRI - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.411
Method	Wald test

Primary: Systemic vascular resistance index - Day 3

End point title	Systemic vascular resistance index - Day 3
End point description:	
End point type	Primary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[3]	22		
Units: dyne*sec*cm^(-5)*m^(-2)				
arithmetic mean (standard deviation)	1837 (± 376)	1831 (± 310)		

Notes:

[3] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis SVRI - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.991
Method	Wald test

Primary: Systemic vascular resistance index - 3 Months

End point title	Systemic vascular resistance index - 3 Months

End point description:

End point type	Primary

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[4]	22		
Units: dyne*sec*cm^(-5)*m^(-2)				
arithmetic mean (standard deviation)	1908 (± 451)	1909 (± 428)		

Notes:

[4] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis SVRI - 3 Months
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.795
Method	Wald test

Primary: Cardiac index - Baseline

End point title	Cardiac index - Baseline

End point description:

End point type	Primary

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[5]	22		
Units: l/min/m²				
arithmetic mean (standard deviation)	3.2 (± 0.6)	3.2 (± 0.6)		

Notes:

[5] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis CI - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.682
Method	Wald test

Primary: Cardiac index - Day 1

End point title	Cardiac index - Day 1

End point description:

End point type	Primary

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[6]	22		
Units: l/min/m²				
arithmetic mean (standard deviation)	3.1 (± 0.5)	3.1 (± 0.5)		

Notes:

[6] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis CI - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771
Method	Wald test

Primary: Cardiac index - Day 3

End point title	Cardiac index - Day 3

End point description:

End point type	Primary

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[7]	22		
Units: l/min/m²				
arithmetic mean (standard deviation)	3.0 (± 0.6)	3.1 (± 0.5)		

Notes:

[7] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis CI - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293
Method	Wald test

Primary: Cardiac index - 3 Months

End point title	Cardiac index - 3 Months
End point description:	
End point type	Primary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[8]	22		
Units: l/min/m²				
arithmetic mean (standard deviation)	3.1 (± 0.5)	3.1 (± 0.5)		

Notes:

[8] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis CI - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.303
Method	Wald test

Secondary: Heart rate - Baseline

End point title	Heart rate - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[9]	22		
Units: bpm				
arithmetic mean (standard deviation)	68 (± 12)	66 (± 13)		

Notes:

[9] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis HR - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.665
Method	Wald test

Secondary: Heart rate - Day 1

End point title	Heart rate - Day 1

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[10]	22		
Units: bpm				
arithmetic mean (standard deviation)	69 (± 13)	65 (± 11)		

Notes:

[10] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis HR - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.122
Method	Wald test

Secondary: Heart rate - Day 3

End point title	Heart rate - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[11]	22		
Units: bpm				
arithmetic mean (standard deviation)	68 (± 14)	66 (± 11)		

Notes:

[11] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis HR - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.717
Method	Wald test

Secondary: Heart rate - 3 Months

End point title	Heart rate - 3 Months
End point description:	
End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[12]	22		
Units: bpm				
arithmetic mean (standard deviation)	67 (± 10)	66 (± 11)		

Notes:

[12] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis HR - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393
Method	Wald test

Secondary: Systolic blood pressure - Baseline

End point title	Systolic blood pressure - Baseline
End point description:	

End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[13]	22		
Units: mmHg				
arithmetic mean (standard deviation)	135 (± 16)	136 (± 18)		

Notes:

[13] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis syst. BP - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.934
Method	Wald test

Secondary: Systolic blood pressure - Day 1

End point title	Systolic blood pressure - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[14]	22		
Units: mmHg				
arithmetic mean (standard deviation)	128 (± 16)	134 (± 16)		

Notes:

[14] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis syst. BP - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279
Method	Wald test

Secondary: Systolic blood pressure - Day 3

End point title	Systolic blood pressure - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[15]	22		
Units: mmHg				
arithmetic mean (standard deviation)	125 (± 16)	133 (± 19)		

Notes:

[15] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis syst. BP - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115
Method	Wald test

Secondary: Systolic blood pressure - 3 Months

End point title	Systolic blood pressure - 3 Months

End point description:

End point type	Secondary

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[16]	22		
Units: mmHg				
arithmetic mean (standard deviation)	128 (± 15)	132 (± 20)		

Notes:

[16] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

Statistical analyses

Statistical analysis title	Analysis syst. BP - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.318
Method	Wald test

Secondary: Diastolic blood pressure - Baseline

End point title	Diastolic blood pressure - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[17]	22		
Units: mmHg				
arithmetic mean (standard deviation)	82 (± 13)	81 (± 14)		

Notes:

[17] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis diast. BP - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.964
Method	Wald test

Secondary: Diastolic blood pressure - Day 1

End point title	Diastolic blood pressure - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[18]	22		
Units: mmHg				
arithmetic mean (standard deviation)	80 (± 11)	80 (± 13)		

Notes:

[18] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis diast. BP - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.876
Method	Wald test

Secondary: Diastolic blood pressure - Day 3

End point title	Diastolic blood pressure - Day 3

End point description:

End point type	Secondary

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[19]	22		
Units: mmHg				
arithmetic mean (standard deviation)	80 (± 9)	80 (± 12)		

Notes:

[19] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis diast. BP - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.925
Method	Wald test

Secondary: Diastolic blood pressure - 3 Months

End point title	Diastolic blood pressure - 3 Months
End point description:	
End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[20]	22		
Units: mmHg				
arithmetic mean (standard deviation)	79 (± 11)	82 (± 11)		

Notes:

[20] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

Statistical analyses

Statistical analysis title	Analysis diast. BP - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.197
Method	Wald test

Secondary: Stroke volume index - Baseline

End point title	Stroke volume index - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[21]	22		
Units: ml/b/m²				
arithmetic mean (standard deviation)	47 (± 7)	50 (± 7)		

Notes:

[21] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis SVI - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	Wald test

Secondary: Stroke volume index - Day 1

End point title	Stroke volume index - Day 1

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[22]	22		
Units: ml/b/m²				
arithmetic mean (standard deviation)	45 (± 8)	48 (± 8)		

Notes:

[22] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis SVI - Day 1
Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.344
Method	Wald test

Secondary: Stroke volume index - Day 3

End point title	Stroke volume index - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[23]	22		
Units: ml/b/m²				
arithmetic mean (standard deviation)	44 (± 8)	48 (± 8)		

Notes:

[23] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis SVI - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	Wald test

Secondary: Stroke volume index - 3 Months

End point title	Stroke volume index - 3 Months
End point description:	
End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[24]	22		
Units: ml/b/m²				
arithmetic mean (standard deviation)	47 (± 7)	47 (± 7)		

Notes:

[24] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis SVI - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.879
Method	Wald test

Secondary: Left ventricular ejection fraction - Baseline

End point title	Left ventricular ejection fraction - Baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[25]	22		
Units: percentage				
arithmetic mean (standard deviation)	51 (± 5.0)	48 (± 6.8)		

Notes:

[25] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV-EF - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.183
Method	Wald test

Secondary: Left ventricular ejection fraction - Day 1

End point title	Left ventricular ejection fraction - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[26]	22		
Units: percentage				
arithmetic mean (standard deviation)	51 (± 4.6)	48 (± 6.2)		

Notes:

[26] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV-EF - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.852
Method	Wald test

Secondary: Left ventricular ejection fraction - Day 3

End point title	Left ventricular ejection fraction - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[27]	22		
Units: percentage				
arithmetic mean (standard deviation)	51 (± 4.7)	48 (± 6.1)		

Notes:

[27] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV-EF - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.333
Method	Wald test

Secondary: Left ventricular ejection fraction - 3 Months

End point title	Left ventricular ejection fraction - 3 Months
End point description:	

End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[28]	22		
Units: percentage				
arithmetic mean (standard deviation)	51 (± 4.4)	48 (± 6.4)		

Notes:

[28] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV-EF - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375
Method	Wald test

Secondary: Left ventricular diastolic function (E/é mean) - Baseline

End point title	Left ventricular diastolic function (E/é mean) - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[29]	21[30]		
Units: none				
arithmetic mean (standard deviation)	9.2 (± 2.6)	9.3 (± 2.2)		

Notes:

[29] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[30] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis E/é mean - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.898
Method	Wald test

Secondary: Left ventricular diastolic function (E/é mean) - Day 1

End point title	Left ventricular diastolic function (E/é mean) - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[31]	22		
Units: none				
arithmetic mean (standard deviation)	8.5 (± 2.2)	10.1 (± 1.4)		

Notes:

[31] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis E/é mean - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Wald test

Secondary: Left ventricular diastolic function (E/é mean) - Day 3

End point title	Left ventricular diastolic function (E/é mean) - Day 3
End point description:	

End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[32]	22		
Units: none				
arithmetic mean (standard deviation)	8.5 (± 2.4)	9.5 (± 1.5)		

Notes:

[32] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis E/é mean - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	Wald test

Secondary: Left ventricular diastolic function (E/é mean) - 3 Months

End point title	Left ventricular diastolic function (E/é mean) - 3 Months
End point description:	
End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[33]	22		
Units: none				
arithmetic mean (standard deviation)	8.3 (± 2.9)	9.7 (± 1.9)		

Notes:

[33] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis E/é mean - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Wald test

Secondary: Left atrial volume index - Baseline

End point title	Left atrial volume index - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[34]	22		
Units: ml/m²				
arithmetic mean (standard deviation)	28 (± 9)	31 (± 11)		

Notes:

[34] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA VI - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414
Method	Wald test

Secondary: Left atrial volume index - Day 1

End point title	Left atrial volume index - Day 1
End point description:	

End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[35]	22		
Units: ml/m²				
arithmetic mean (standard deviation)	26 (± 10)	30 (± 13)		

Notes:

[35] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA VI - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Wald test

Secondary: Left atrial volume index - Day 3

End point title	Left atrial volume index - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[36]	22		
Units: ml/m²				
arithmetic mean (standard deviation)	28 (± 10)	30 (± 13)		

Notes:

[36] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA VI - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Wald test

Secondary: Left atrial volume index - 3 Months

End point title	Left atrial volume index - 3 Months
End point description:	
End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[37]	22		
Units: ml/m²				
arithmetic mean (standard deviation)	26 (± 9)	31 (± 12)		

Notes:

[37] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA VI - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239
Method	Wald test

Secondary: Mitral E-wave velocity - Baseline

End point title	Mitral E-wave velocity - Baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[38]	21[39]		
Units: m/sec				
arithmetic mean (standard deviation)	0.80 (± 0.20)	0.78 (± 0.14)		

Notes:

[38] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[39] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis E - Baseline
Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.686
Method	Wald test

Secondary: Mitral E-wave velocity - Day 1

End point title	Mitral E-wave velocity - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[40]	22		
Units: m/sec				
arithmetic mean (standard deviation)	0.73 (± 0.20)	0.80 (± 0.12)		

Notes:

[40] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis E - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Wald test

Secondary: Mitral E-wave velocity - Day 3

End point title	Mitral E-wave velocity - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[41]	22		
Units: m/sec				
arithmetic mean (standard deviation)	0.72 (± 0.18)	0.78 (± 0.11)		

Notes:

[41] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis E - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Wald test

Secondary: Mitral E-wave velocity - 3 Months

End point title	Mitral E-wave velocity - 3 Months

End point description:

End point type	Secondary

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[42]	22		
Units: m/sec				
arithmetic mean (standard deviation)	0.72 (± 0.21)	0.78 (± 0.13)		

Notes:

[42] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis E - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wald test

Secondary: Glucose serum level - Baseline

End point title	Glucose serum level - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[43]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	181 (± 75)	175 (± 52)		

Notes:

[43] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Glucose - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742
Method	Wald test

Secondary: Glucose serum level - Day 1

End point title	Glucose serum level - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[44]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	152 (± 38)	171 (± 48)		

Notes:

[44] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Glucose - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Wald test

Secondary: Glucose serum level - Day 3

End point title	Glucose serum level - Day 3

End point description:

End point type	Secondary

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[45]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	146 (± 35)	166 (± 52)		

Notes:

[45] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis Glucose - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Wald test

Secondary: Glucose serum level - 3 Months

End point title	Glucose serum level - 3 Months
End point description:	
End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[46]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	150 (± 41)	156 (± 52)		

Notes:

[46] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis Glucose - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.754
Method	Wald test

Secondary: HbA1c serum level - Baseline

End point title	HbA1c serum level - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[47]	22		
Units: percentage				
arithmetic mean (standard deviation)	7.5 (± 0.9)	7.9 (± 1.3)		

Notes:

[47] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis HbA1c - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.228
Method	Wald test

Secondary: HbA1c serum leven - Day 1

End point title	HbA1c serum leven - Day 1
End point description:	

End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[48]	22		
Units: percentage				
arithmetic mean (standard deviation)	7.4 (± 0.9)	7.9 (± 1.3)		

Notes:

[48] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis HbA1c - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.722
Method	Wald test

Secondary: HbA1c serum level - Day 3

End point title	HbA1c serum level - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[49]	20[50]		
Units: percentage				
arithmetic mean (standard deviation)	7.4 (± 0.9)	7.9 (± 1.2)		

Notes:

[49] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

[50] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis HbA1c - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Wald test

Secondary: HbA1c serum level - 3 Months

End point title	HbA1c serum level - 3 Months
End point description:	
End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[51]	22		
Units: percentage				
arithmetic mean (standard deviation)	7.2 (± 0.7)	7.8 (± 1.5)		

Notes:

[51] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis HbA1c - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.595
Method	Wald test

Secondary: Cystatin C serum level - Baseline

End point title	Cystatin C serum level - Baseline
End point description:	

End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[52]	22		
Units: mg/l				
arithmetic mean (standard deviation)	1.2 (± 0.4)	1.0 (± 0.2)		

Notes:

[52] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Cystatin C - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	Wald test

Secondary: Cystatin C serum level - Day 1

End point title	Cystatin C serum level - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[53]	22		
Units: mg/l				
arithmetic mean (standard deviation)	1.3 (± 0.4)	1.0 (± 0.2)		

Notes:

[53] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Cystatin C - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wald test

Secondary: Cystatin C serum level - Day 3

End point title	Cystatin C serum level - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[54]	22		
Units: mg/l				
arithmetic mean (standard deviation)	1.3 (± 0.4)	1.0 (± 0.2)		

Notes:

[54] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis Cystatin C - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wald test

Secondary: Cystatin C serum level - 3 Months

End point title	Cystatin C serum level - 3 Months

End point description:

End point type	Secondary

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[55]	22		
Units: mg/l				
arithmetic mean (standard deviation)	1.3 (± 0.4)	1.0 (± 0.2)		

Notes:

[55] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis Cystatin C - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wald test

Secondary: NT-proBNP serum level - Baseline

End point title	NT-proBNP serum level - Baseline
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[56]	22		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	239 (91 to 463)	166 (73 to 238)		

Notes:

[56] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis NT-proBNP - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.481
Method	Wald test

Secondary: NT-proBNP serum level - Day 1

End point title	NT-proBNP serum level - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[57]	22		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	192 (63 to 385)	168 (67 to 252)		

Notes:

[57] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis NT-proBNP - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.224
Method	Wald test

Secondary: NT-proBNP serum level - Day 3

End point title	NT-proBNP serum level - Day 3

End point description:

End point type	Secondary

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[58]	22		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	173 (57 to 402)	147 (58 to 226)		

Notes:

[58] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis NT-proBNP - Day 3
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.408
Method	Wald test

Secondary: NT-proBNP serum level - 3 Months

End point title	NT-proBNP serum level - 3 Months

End point description:

End point type	Secondary

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[59]	20[60]		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	120 (34 to 356)	158 (42 to 262)		

Notes:

[59] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

[60] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis NT-proBNP - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723
Method	Wald test

Secondary: Aldosterone serum level - Baseline

End point title	Aldosterone serum level - Baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[61]	22		
Units: pg/ml				
arithmetic mean (standard deviation)	104 (± 65)	83 (± 33)		

Notes:

[61] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Aldosterone - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213
Method	Wald test

Secondary: Aldosterone serum level - Day 1

End point title	Aldosterone serum level - Day 1

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[62]	22		
Units: pg/ml				
arithmetic mean (standard deviation)	111 (± 67)	88 (± 32)		

Notes:

[62] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Aldosterone - Day 1
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.825
Method	Wald test

Secondary: Aldosterone serum level - Day 3

End point title	Aldosterone serum level - Day 3
End point description:	

End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[63]	22		
Units: pg/ml				
arithmetic mean (standard deviation)	108 (± 59)	96 (± 50)		

Notes:

[63] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis Aldosterone - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.635
Method	Wald test

Secondary: Aldosterone serum level - 3 Months

End point title	Aldosterone serum level - 3 Months
End point description:	

End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[64]	22		
Units: pg/ml				
arithmetic mean (standard deviation)	137 (± 104)	108 (± 71)		

Notes:

[64] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis Aldosterone - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.522
Method	Wald test

Secondary: Sodium urine excretion - Baseline

End point title	Sodium urine excretion - Baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[65]	20[66]		
Units: mmol/24hrs				
arithmetic mean (standard deviation)	164 (± 88)	196 (± 84)		

Notes:

[65] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[66] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis Sodium excretion - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.255
Method	Wald test

Secondary: Sodium urine excretion - Day 1

End point title	Sodium urine excretion - Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[67]	21[68]		
Units: mmol/24hrs				
arithmetic mean (standard deviation)	185 (± 111)	181 (± 76)		

Notes:

[67] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[68] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis Sodium excretion - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.223
Method	Wald test

Secondary: Sodium urine excretion - Day 3

End point title	Sodium urine excretion - Day 3
End point description:	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[69]	21[70]		
Units: mmol/24hrs				
arithmetic mean (standard deviation)	181 (± 126)	203 (± 107)		

Notes:

[69] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

[70] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis Sodium excretion - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	Wald test

Secondary: Sodium urine excretion - 3 Months

End point title	Sodium urine excretion - 3 Months
End point description:	

End point type	Secondary
End point timeframe:	

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[71]	20[72]		
Units: mmol/24hrs				
arithmetic mean (standard deviation)	201 (± 145)	175 (± 55)		

Notes:

[71] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[72] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis Sodium excretion - 3 Months
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Wald test

Secondary: Glucose urine excretion - Baseline

End point title	Glucose urine excretion - Baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[73]	20[74]		
Units: g/24hrs				
arithmetic mean (standard deviation)	7.3 (± 22.7)	10.9 (± 22.7)		

Notes:

[73] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[74] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis Glucose excretion - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.617
Method	Wald test

Secondary: Glucose urine excretion - Day 1

End point title	Glucose urine excretion - Day 1

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[75]	21[76]		
Units: g/24hrs				
arithmetic mean (standard deviation)	48.4 (± 34.7)	6.9 (± 14.1)		

Notes:

[75] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[76] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis Glucose excretion - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wald test

Secondary: Glucose urine excretion - Day 3

End point title	Glucose urine excretion - Day 3

End point description:

End point type	Secondary

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[77]	21[78]		
Units: g/24hrs				
arithmetic mean (standard deviation)	65.7 (± 43.3)	7.5 (± 14.5)		

Notes:

[77] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

[78] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis Glucose excretion - Day 3
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wald test

Secondary: Glucose urine excretion - 3 Months

End point title	Glucose urine excretion - 3 Months
End point description:	

End point type	Secondary
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[79]	20[80]		
Units: g/24hrs				
arithmetic mean (standard deviation)	67.6 (± 50.9)	10.2 (± 18.7)		

Notes:

[79] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[80] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis Glucose excretion - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wald test

Post-hoc: Total cholesterol serum level - Baseline

End point title	Total cholesterol serum level - Baseline
End point description:	

End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[81]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	169 (± 41)	155 (± 39)		

Notes:

[81] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Total Cholesterol - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.257
Method	Wald test

Post-hoc: Total cholesterol serum level - Day 1

End point title	Total cholesterol serum level - Day 1
End point description:	

End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[82]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	174 (± 43)	155 (± 37)		

Notes:

[82] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Total Cholesterol - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.178
Method	Wald test

Post-hoc: Total cholesterol serum level - Day 3

End point title	Total cholesterol serum level - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[83]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	168 (± 39)	152 (± 40)		

Notes:

[83] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis Total Cholesterol - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.824
Method	Wald test

Post-hoc: Total cholesterol serum level - 3 Months

End point title	Total cholesterol serum level - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[84]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	185 (± 48)	152 (± 42)		

Notes:

[84] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis Total Cholesterol - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.001
Method	Wald test

Post-hoc: LDL-C serum level - Baseline

End point title	LDL-C serum level - Baseline
End point description:	

End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[85]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	103 (± 36)	95 (± 38)		

Notes:

[85] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis LDL-C - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.522
Method	Wald test

Post-hoc: LDL-C serum level - Day 1

End point title	LDL-C serum level - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[86]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	102 (± 36)	94 (± 36)		

Notes:

[86] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis LDL-C - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.915
Method	Wald test

Post-hoc: LDL-C serum level - Day 3

End point title	LDL-C serum level - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[87]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	102 (± 40)	93 (± 39)		

Notes:

[87] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LDL-C - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.477
Method	Wald test

Post-hoc: LDL-C serum level - 3 Months

End point title	LDL-C serum level - 3 Months
End point description:	

End point type	Post-hoc
End point timeframe:	

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[88]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	112 (± 47)	89 (± 39)		

Notes:

[88] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LDL-C - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001
Method	Wald test

Post-hoc: HDL-C serum level - Baseline

End point title	HDL-C serum level - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[89]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	43 (± 9)	44 (± 9)		

Notes:

[89] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis HDL-C - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.53
Method	Wald test

Post-hoc: HDL-C serum level - Day 1

End point title	HDL-C serum level - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[90]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	42 (± 10)	44 (± 9)		

Notes:

[90] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis HDL-C - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.947
Method	Wald test

Post-hoc: HDL-C serum level - Day 3

End point title	HDL-C serum level - Day 3

End point description:

End point type	Post-hoc

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[91]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	43 (± 9)	44 (± 9)		

Notes:

[91] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis HDL-C - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.9
Method	Wald test

Post-hoc: HDL-C serum level - 3 Months

End point title	HDL-C serum level - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[92]	22		
Units: mg/dl				
arithmetic mean (standard deviation)	46 (± 10)	46 (± 11)		

Notes:

[92] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis HDL-C - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.937
Method	Wald test

Post-hoc: eGFR - Baseline

End point title	eGFR - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[93]	22		
Units: ml/min/1.73m²				
arithmetic mean (standard deviation)	77 (± 21)	88 (± 16)		

Notes:

[93] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis eGFR - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.076
Method	Wald test

Post-hoc: eGFR - Day 1

End point title	eGFR - Day 1

End point description:

End point type	Post-hoc

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[94]	22		
Units: ml/min/1.73m²				
arithmetic mean (standard deviation)	70 (± 19)	85 (± 16)		

Notes:

[94] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis eGFR - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.014
Method	Wald test

Post-hoc: eGFR - Day 3

End point title	eGFR - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[95]	22		
Units: ml/min/1.73m²				
arithmetic mean (standard deviation)	70 (± 21)	85 (± 17)		

Notes:

[95] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis eGFR - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.039
Method	Wald test

Post-hoc: eGFR - 3 Months

End point title	eGFR - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[96]	22		
Units: ml/min/1.73m²				
arithmetic mean (standard deviation)	68 (± 20)	85 (± 16)		

Notes:

[96] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis eGFR - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.108
Method	Wald test

Post-hoc: Hemoglobin - Baseline

End point title	Hemoglobin - Baseline

End point description:

End point type	Post-hoc

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[97]	22		
Units: g/dl				
arithmetic mean (standard deviation)	13.7 (± 1.8)	14.3 (± 1.3)		

Notes:

[97] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Hemoglobin - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.299
Method	Wald test

Post-hoc: Hemoglobin - Day 1

End point title	Hemoglobin - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[98]	22		
Units: g/dl				
arithmetic mean (standard deviation)	13.7 (± 1.9)	14.1 (± 1.2)		

Notes:

[98] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Hemoglobin - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.487
Method	Wald test

Post-hoc: Hemoglobin - Day 3

End point title	Hemoglobin - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[99]	22		
Units: g/dl				
arithmetic mean (standard deviation)	13.2 (± 1.8)	14.0 (± 1.4)		

Notes:

[99] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis Hemoglobin - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.685
Method	Wald test

Post-hoc: Hemoglobin - 3 Months

End point title	Hemoglobin - 3 Months
End point description:	

End point type	Post-hoc
End point timeframe:	

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[100]	22		
Units: g/dl				
arithmetic mean (standard deviation)	14.2 (± 2.4)	14.2 (± 1.7)		

Notes:

[100] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis Hemoglobin - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.005
Method	Wald test

Post-hoc: Hematocrit - Baseline

End point title	Hematocrit - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[101]	22		
Units: percentage				
arithmetic mean (standard deviation)	41.0 (± 4.5)	42.4 (± 3.4)		

Notes:

[101] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Hematocrit - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.284
Method	Wald test

Post-hoc: Hematocrit - Day 1

End point title	Hematocrit - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[102]	22		
Units: percentage				
arithmetic mean (standard deviation)	40.9 (± 4.6)	42.1 (± 3.5)		

Notes:

[102] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis Hematocrit - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.761
Method	Wald test

Post-hoc: Hematocrit - Day 3

End point title	Hematocrit - Day 3
End point description:	

End point type	Post-hoc
End point timeframe:	

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[103]	22		
Units: percentage				
arithmetic mean (standard deviation)	39.9 (± 4.5)	41.5 (± 3.7)		

Notes:

[103] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis Hematocrit - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.93
Method	Wald test

Post-hoc: Hematocrit - 3 Months

End point title	Hematocrit - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[104]	22		
Units: percentage				
arithmetic mean (standard deviation)	43.3 (± 5.6)	42.3 (± 4.6)		

Notes:

[104] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis Hematocrit - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001
Method	Wald test

Post-hoc: Urinary volume - Baseline

End point title	Urinary volume - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[105]	20[106]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	1740 (± 601)	1788 (± 756)		

Notes:

[105] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[106] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis Urinary volume - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.829
Method	Wald test

Post-hoc: Urinary volume - Day 1

End point title	Urinary volume - Day 1

End point description:

End point type	Post-hoc

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[107]	21[108]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	2112 (± 837)	1626 (± 681)		

Notes:

[107] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[108] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis Urinary volume - Day 1
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.011
Method	Wald test

Post-hoc: Urinary volume - Day 3

End point title	Urinary volume - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[109]	21[110]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	2111 (± 758)	2007 (± 913)		

Notes:

[109] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data
[110] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis Urinary volume - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.429
Method	Wald test

Post-hoc: Urinary volume - 3 Months

End point title	Urinary volume - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[111]	21[112]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	2319 (± 873)	1664 (± 594)		

Notes:

[111] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[112] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis Urinary volume - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.001
Method	Wald test

Post-hoc: Electrolyte-free water clearance - Baseline

End point title	Electrolyte-free water clearance - Baseline

End point description:

End point type	Post-hoc

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[113]	20[114]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	166 (± 830)	-15 (± 721)		

Notes:

[113] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[114] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis EF WC - Baseline
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.467
Method	Wald test

Post-hoc: Electrolyte-free water clearance - Day 1

End point title	Electrolyte-free water clearance - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[115]	21[116]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	417 (± 802)	-124 (± 654)		

Notes:

[115] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

[116] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis EF WC - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.011
Method	Wald test

Post-hoc: Electrolyte-free water clearance - Day 3

End point title	Electrolyte-free water clearance - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[117]	21[118]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	461 (± 551)	90 (± 874)		

Notes:

[117] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

[118] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis EF WC - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.07
Method	Wald test

Post-hoc: Electrolyte-free water clearance - 3 Months

End point title	Electrolyte-free water clearance - 3 Months

End point description:

End point type	Post-hoc

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[119]	20[120]		
Units: ml/24hrs				
arithmetic mean (standard deviation)	380 (± 765)	-91 (± 597)		

Notes:

[119] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[120] - 2 missing data

Statistical analyses

Statistical analysis title	Analysis EF WC - 3 Months
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	36
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.013
Method	Wald test

Post-hoc: Left ventricular enddiastolic diameter - Baseline

End point title	Left ventricular enddiastolic diameter - Baseline

End point description:

End point type	Post-hoc

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[121]	22		
Units: mm				
arithmetic mean (standard deviation)	49 (± 5)	50 (± 5)		

Notes:

[121] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVEDD - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.365
Method	Wald test

Post-hoc: Left ventricular enddiastolic diameter - Day 1

End point title	Left ventricular enddiastolic diameter - Day 1

End point description:

End point type	Post-hoc

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[122]	22		
Units: mm				
arithmetic mean (standard deviation)	49 (± 5)	50 (± 6)		

Notes:

[122] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVEDD - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.864
Method	Wald test

Post-hoc: Left ventricular enddiastolic diameter - Day 3

End point title	Left ventricular enddiastolic diameter - Day 3

End point description:

End point type	Post-hoc

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[123]	22		
Units: mm				
arithmetic mean (standard deviation)	48 (± 5)	49 (± 5)		

Notes:

[123] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVEDD - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.449
Method	Wald test

Post-hoc: Left ventricular enddiastolic diameter - 3 Months

End point title	Left ventricular enddiastolic diameter - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[124]	22		
Units: mm				
arithmetic mean (standard deviation)	48 (± 6)	50 (± 6)		

Notes:

[124] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVEDD - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.994
Method	Wald test

Post-hoc: Left ventricular endsystolic diameter - Baseline

End point title	Left ventricular endsystolic diameter - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[125]	22		
Units: mm				
arithmetic mean (standard deviation)	34 (± 6)	36 (± 8)		

Notes:

[125] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVESD - Baseline
Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.386
Method	Wald test

Post-hoc: Left ventricular endsystolic diameter - Day 1

End point title	Left ventricular endsystolic diameter - Day 1
End point description:	

End point type	Post-hoc
End point timeframe:	

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[126]	22		
Units: mm				
arithmetic mean (standard deviation)	35 (± 5)	36 (± 9)		

Notes:

[126] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVESD - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.595
Method	Wald test

Post-hoc: Left ventricular endsystolic diameter - Day 3

End point title	Left ventricular endsystolic diameter - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[127]	22		
Units: mm				
arithmetic mean (standard deviation)	34 (± 5)	35 (± 8)		

Notes:

[127] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVESD - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.187
Method	Wald test

Post-hoc: Left ventricular endsystolic diameter - 3 Months

End point title	Left ventricular endsystolic diameter - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[128]	22		
Units: mm				
arithmetic mean (standard deviation)	33 (± 6)	37 (± 8)		

Notes:

[128] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LVESD - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.284
Method	Wald test

Post-hoc: Interventricular septum in diastole - Baseline

End point title	Interventricular septum in diastole - Baseline
End point description:	

End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[129]	22		
Units: mm				
arithmetic mean (standard deviation)	10 (± 1)	10 (± 2)		

Notes:

[129] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis IVSd - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.94
Method	Wald test

Post-hoc: Interventricular septum in diastole - Day 1

End point title	Interventricular septum in diastole - Day 1
End point description:	

End point type	Post-hoc

End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[130]	22		
Units: mm				
arithmetic mean (standard deviation)	11 (± 2)	10 (± 2)		

Notes:

[130] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis IVSd - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.764
Method	Wald test

Post-hoc: Interventricular septum in diastole - Day 3

End point title	Interventricular septum in diastole - Day 3
End point description:	

End point type	Post-hoc

End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[131]	22		
Units: mm				
arithmetic mean (standard deviation)	11 (± 2)	10 (± 2)		

Notes:

[131] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis IVSd - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.63
Method	Wald test

Post-hoc: Interventricular septum in diastole - 3 Months

End point title	Interventricular septum in diastole - 3 Months
End point description:	

End point type	Post-hoc
End point timeframe:	

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[132]	22		
Units: mm				
arithmetic mean (standard deviation)	10 (± 1)	10 (± 2)		

Notes:

[132] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis IVSd - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.497
Method	Wald test

Post-hoc: Left ventricular mass index - Baseline

End point title	Left ventricular mass index - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[133]	22		
Units: g/m²				
arithmetic mean (standard deviation)	86 (± 19)	91 (± 21)		

Notes:

[133] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV MI - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.474
Method	Wald test

Post-hoc: Left ventricular mass index - Day 1

End point title	Left ventricular mass index - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[134]	22		
Units: g/m²				
arithmetic mean (standard deviation)	87 (± 19)	94 (± 24)		

Notes:

[134] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV MI - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.448
Method	Wald test

Post-hoc: Left ventricular mass index - Day 3

End point title	Left ventricular mass index - Day 3
End point description:	

End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[135]	22		
Units: g/m²				
arithmetic mean (standard deviation)	84 (± 19)	90 (± 21)		

Notes:

[135] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV MI - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.701
Method	Wald test

Post-hoc: Left ventricular mass index - 3 Months

End point title	Left ventricular mass index - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[136]	22		
Units: g/m²				
arithmetic mean (standard deviation)	84 (± 17)	89 (± 23)		

Notes:

[136] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LV MI - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.807
Method	Wald test

Post-hoc: Left atrial area - Baseline

End point title	Left atrial area - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[137]	22		
Units: cm²				
arithmetic mean (standard deviation)	20 (± 3.7)	20 (± 4.2)		

Notes:

[137] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA area - Baseline
Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.484
Method	Wald test

Post-hoc: Left atrial area - Day 1

End point title	Left atrial area - Day 1
End point description:	

End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[138]	22		
Units: cm²				
arithmetic mean (standard deviation)	18 (± 4.3)	20 (± 5.3)		

Notes:

[138] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA area - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.082
Method	Wald test

Post-hoc: Left atrial area - Day 3

End point title	Left atrial area - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[139]	22		
Units: cm²				
arithmetic mean (standard deviation)	19 (± 4.8)	20 (± 5.7)		

Notes:

[139] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA area - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.691
Method	Wald test

Post-hoc: Left atrial area - 3 Months

End point title	Left atrial area - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[140]	22		
Units: cm²				
arithmetic mean (standard deviation)	18 (± 4.0)	20 (± 4.1)		

Notes:

[140] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis LA area - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.503
Method	Wald test

Post-hoc: Mitral A-wave velocity - Baseline

End point title	Mitral A-wave velocity - Baseline

End point description:

End point type	Post-hoc

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[141]	21[142]		
Units: m/sec				
arithmetic mean (standard deviation)	0.82 (± 0.17)	0.73 (± 0.17)		

Notes:

[141] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data
[142] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis A - Baseline
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.095
Method	Wald test

Post-hoc: Mitral A-wave velocity - Day 1

End point title	Mitral A-wave velocity - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[143]	21[144]		
Units: m/sec				
arithmetic mean (standard deviation)	0.81 (± 0.15)	0.74 (± 0.20)		

Notes:

[143] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[144] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis A - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.786
Method	Wald test

Post-hoc: Mitral A-wave velocity - Day 3

End point title	Mitral A-wave velocity - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[145]	22		
Units: m/sec				
arithmetic mean (standard deviation)	0.80 (± 0.15)	0.75 (± 0.19)		

Notes:

[145] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 5 missing data

Statistical analyses

Statistical analysis title	Analysis A - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.55
Method	Wald test

Post-hoc: Mitral A-wave velocity - 3 Months

End point title	Mitral A-wave velocity - 3 Months
End point description:	

End point type	Post-hoc
End point timeframe:	

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[146]	22		
Units: m/sec				
arithmetic mean (standard deviation)	0.83 (± 0.15)	0.73 (± 0.20)		

Notes:

[146] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 6 missing data

Statistical analyses

Statistical analysis title	Analysis A - 3 Months
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	36
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.927
Method	Wald test

Post-hoc: E/A ratio - Baseline

End point title	E/A ratio - Baseline

End point description:

End point type	Post-hoc

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[147]	21[148]		
Units: none				
arithmetic mean (standard deviation)	0.97 (± 0.22)	1.18 (± 0.53)		

Notes:

[147] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

[148] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis E/A - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.121
Method	Wald test

Post-hoc: E/A ratio - Day 1

End point title	E/A ratio - Day 1

End point description:

End point type	Post-hoc

End point timeframe:

Day 1

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[149]	21[150]		
Units: none				
arithmetic mean (standard deviation)	0.88 (± 0.20)	1.20 (± 0.55)		

Notes:

[149] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[150] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis E/A - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.042
Method	Wald test

Post-hoc: E/A ratio - Day 3

End point title	E/A ratio - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[151]	22		
Units: none				
arithmetic mean (standard deviation)	0.89 (± 0.23)	1.16 (± 0.58)		

Notes:

[151] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 5 missing data

Statistical analyses

Statistical analysis title	Analysis E/A - Day 3
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.181
Method	Wald test

Post-hoc: E/A ratio - 3 Months

End point title	E/A ratio - 3 Months

End point description:

End point type	Post-hoc

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[152]	22		
Units: none				
arithmetic mean (standard deviation)	0.85 (± 0.23)	1.21 (± 0.52)		

Notes:

[152] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 6 missing data

Statistical analyses

Statistical analysis title	Analysis E/A - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	36
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.038
Method	Wald test

Post-hoc: Mitral annular velocity e' septal - Baseline

End point title	Mitral annular velocity e' septal - Baseline

End point description:

End point type	Post-hoc

End point timeframe:

Baseline

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[153]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	7.5 (± 1.9)	7.2 (± 1.7)		

Notes:

[153] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis e' septal - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.603
Method	Wald test

Post-hoc: Mitral annular velocity e' septal - Day 1

End point title	Mitral annular velocity e' septal - Day 1
End point description:	

End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[154]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	7.8 (± 2.1)	6.6 (± 2.0)		

Notes:

[154] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis e' septal - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.077
Method	Wald test

Post-hoc: Mitral annular velocity e' septal - Day 3

End point title	Mitral annular velocity e' septal - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[155]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	7.5 (± 2.0)	7.2 (± 1.6)		

Notes:

[155] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis e' septal - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.785
Method	Wald test

Post-hoc: Mitral annular velocity e' septal - 3 Months

End point title	Mitral annular velocity e' septal - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[156]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	7.8 (± 2.1)	7.2 (± 1.6)		

Notes:

[156] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis e' septal - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.47
Method	Wald test

Post-hoc: Mitral annular velocity e' lateral - Baseline

End point title	Mitral annular velocity e' lateral - Baseline
End point description:	

End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[157]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	10.4 (± 1.8)	9.8 (± 2.0)		

Notes:

[157] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis e' lateral - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.319
Method	Wald test

Post-hoc: Mitral annular velocity e' lateral - Day 1

End point title	Mitral annular velocity e' lateral - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[158]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	10.1 (± 2.4)	9.6 (± 2.4)		

Notes:

[158] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis e' lateral - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.97
Method	Wald test

Post-hoc: Mitral annular velocity e' lateral - Day 3

End point title	Mitral annular velocity e' lateral - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[159]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	9.8 (± 2.3)	9.5 (± 1.9)		

Notes:

[159] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis e' lateral - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.84
Method	Wald test

Post-hoc: Mitral annular velocity e' lateral - 3 Months

End point title	Mitral annular velocity e' lateral - 3 Months
End point description:	

End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[160]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	10.4 (± 2.9)	9.3 (± 2.0)		

Notes:

[160] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis e' lateral - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.262
Method	Wald test

Post-hoc: Mitral annular velocity e' mean - Baseline

End point title	Mitral annular velocity e' mean - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[161]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	8.9 (± 1.6)	8.5 (± 1.5)		

Notes:

[161] - 2 subjects were retrospectively excluded from analysis due to protocol deviations

Statistical analyses

Statistical analysis title	Analysis e' mean - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.361
Method	Wald test

Post-hoc: Mitral annular velocity e' mean - Day 1

End point title	Mitral annular velocity e' mean - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[162]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	8.9 (± 2.1)	8.1 (± 1.8)		

Notes:

[162] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis e' mean - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.352
Method	Wald test

Post-hoc: Mitral annular velocity e' mean - Day 3

End point title	Mitral annular velocity e' mean - Day 3
End point description:	

End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[163]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	8.7 (± 2.0)	8.4 (± 1.3)		

Notes:

[163] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 1 missing data

Statistical analyses

Statistical analysis title	Analysis e' mean - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.968
Method	Wald test

Post-hoc: Mitral annular velocity e' mean - 3 Months

End point title	Mitral annular velocity e' mean - 3 Months
End point description:	
End point type	Post-hoc
End point timeframe:	
3 Months	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[164]	22		
Units: cm/sec				
arithmetic mean (standard deviation)	9.1 (± 2.3)	8.3 (± 1.5)		

Notes:

[164] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 3 missing data

Statistical analyses

Statistical analysis title	Analysis e' mean - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.28
Method	Wald test

Post-hoc: Deceleration time - Baseline

End point title	Deceleration time - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[165]	21[166]		
Units: msec				
arithmetic mean (standard deviation)	209 (± 47)	198 (± 54)		

Notes:

[165] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

[166] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis DT - Baseline
Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.61
Method	Wald test

Post-hoc: Deceleration time - Day 1

End point title	Deceleration time - Day 1
End point description:	

End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[167]	22		
Units: msec				
arithmetic mean (standard deviation)	212 (± 35)	189 (± 45)		

Notes:

[167] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

Statistical analyses

Statistical analysis title	Analysis DT - Day 1
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.234
Method	Wald test

Post-hoc: Deceleration time - Day 3

End point title	Deceleration time - Day 3

End point description:

End point type	Post-hoc

End point timeframe:

Day 3

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[168]	22		
Units: msec				
arithmetic mean (standard deviation)	218 (± 42)	202 (± 54)		

Notes:

[168] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

Statistical analyses

Statistical analysis title	Analysis DT - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.624
Method	Wald test

Post-hoc: Deceleration time - 3 Months

End point title	Deceleration time - 3 Months

End point description:

End point type	Post-hoc

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[169]	22		
Units: msec				
arithmetic mean (standard deviation)	213 (± 61)	196 (± 59)		

Notes:

[169] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 2 missing data

Statistical analyses

Statistical analysis title	Analysis DT - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.261
Method	Wald test

Post-hoc: Global longitudinal strain - Baseline

End point title	Global longitudinal strain - Baseline
End point description:	

End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[170]	21[171]		
Units: none				
arithmetic mean (standard deviation)	-19 (± 4.1)	-17 (± 5.3)		

Notes:

[170] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data
[171] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis GLS - Baseline
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.107
Method	Wald test

Post-hoc: Global longitudinal strain - Day 1

End point title	Global longitudinal strain - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[172]	21[173]		
Units: none				
arithmetic mean (standard deviation)	-19 (± 3.4)	-17 (± 4.8)		

Notes:

[172] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[173] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis GLS - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.877
Method	Wald test

Post-hoc: Global longitudinal strain - Day 3

End point title	Global longitudinal strain - Day 3
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[174]	21[175]		
Units: none				
arithmetic mean (standard deviation)	-19 (± 3.7)	-17 (± 4.4)		

Notes:

[174] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[175] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis GLS - Day 3
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.735
Method	Wald test

Post-hoc: Global longitudinal strain - 3 Months

End point title	Global longitudinal strain - 3 Months

End point description:

End point type	Post-hoc

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[176]	21[177]		
Units: none				
arithmetic mean (standard deviation)	-19 (± 2.7)	-17 (± 4.6)		

Notes:

[176] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 4 missing data

[177] - 1 missing data

Statistical analyses

Statistical analysis title	Analysis GLS - 3 Months
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.608
Method	Wald test

Post-hoc: Right ventricular systolic pressure - Baseline

End point title	Right ventricular systolic pressure - Baseline
End point description:	
End point type	Post-hoc
End point timeframe:	
Baseline	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[178]	11[179]		
Units: mmHg				
arithmetic mean (standard deviation)	29 (± 4)	28 (± 6)		

Notes:

[178] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 8 missing data
[179] - 11 missing data

Statistical analyses

Statistical analysis title	Analysis RVSP - Baseline
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	23
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.515
Method	Wald test

Post-hoc: Right ventricular systolic pressure - Day 1

End point title	Right ventricular systolic pressure - Day 1
End point description:	
End point type	Post-hoc
End point timeframe:	
Day 1	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[180]	12[181]		
Units: mmHg				
arithmetic mean (standard deviation)	26 (± 6)	26 (± 5)		

Notes:

[180] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 10 missing data

[181] - 10 missing data

Statistical analyses

Statistical analysis title	Analysis RVSP - Day 1
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	22
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.827
Method	Wald test

Post-hoc: Right ventricular systolic pressure - Day 3

End point title	Right ventricular systolic pressure - Day 3
End point description:	

End point type	Post-hoc
End point timeframe:	
Day 3	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[182]	12[183]		
Units: mmHg				
arithmetic mean (standard deviation)	29 (± 10)	25 (± 4)		

Notes:

[182] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 9 missing data

[183] - 10 missing data

Statistical analyses

Statistical analysis title	Analysis RVSP - Day 3
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	23
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.261
Method	Wald test

Post-hoc: Right ventricular systolic pressure - 3 Months

End point title	Right ventricular systolic pressure - 3 Months

End point description:

End point type	Post-hoc

End point timeframe:

3 Months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[184]	8[185]		
Units: mmHg				
arithmetic mean (standard deviation)	26 (± 11)	27 (± 8)		

Notes:

[184] - 2 subjects were retrospectively excluded from analysis due to protocol deviations; 8 missing data
[185] - 14 missing data

Statistical analyses

Statistical analysis title	Analysis RVSP - 3 Months
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.632
Method	Wald test

Adverse events

Adverse events information

Timeframe for reporting adverse events: 3 Months	
Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	0

Reporting groups

Reporting group title	Empagliflozin
Reporting group description: Subjects in the Empagliflozin arm receive 10 mg tablets Empagliflozin once daily for 3 months.	
Reporting group title	Placebo
Reporting group description: Subjects in the Placebo arm receive one tablet once daily for 3 months.	

Serious adverse events	Empagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	1 / 22 (4.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hematoma in freshly operated knee with suspected inflammation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall from roof with hospitalization for polytrauma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Syncope			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Small segmental pulmonary emboli		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac disorders		
Atrial fibrillation		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Short reanimation		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nervous system disorders		
Vigilance reduction & neurological symptoms		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Blood and lymphatic system disorders		
Hospitalization for clarification of the Hb drop		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
General disorders and administration site conditions		
Discomfort		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatobiliary disorders		
Acute cholecystitis with stationary gallbladder surgery		

	Empagliflozin	Placebo	
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
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			
Multiple fractures			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (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: 0 %

Non-serious adverse events	Empagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 22 (86.36%)	17 / 22 (77.27%)	
Vascular disorders			
Edema			
subjects affected / exposed	3 / 22 (13.64%)	3 / 22 (13.64%)	
occurrences (all)	3	3	
Orthostatic hypotension			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Pale skin color			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Planned outpatient meniscus knee surgery			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Gynecomastia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Psychiatric disorders			
Depressive Mood			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Scratch marks after gardening			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Aggravation of chronic right heart strain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Asymptomatic AV block grade IIa Wenkebach			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
AV block grade I			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Hypertensive emergency with chest pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
left ventricular thrombus on ultrasound cardiogram			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
NT-proBNP increase			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Nervous system disorders			
Tingling			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Blood Eosinophilia of unknown origin			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Hb drop of unclear origin			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Leucocytosis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystothiliasis			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Newly diagnosed liver cirrhosis on sonography, without elevation of liver enzymes			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Steatosis hepatis			
subjects affected / exposed	3 / 22 (13.64%)	4 / 22 (18.18%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Balantitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Change of fingernails			

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Generalized pruritus in the genital area

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders

increased urge to urinate

subjects affected / exposed	3 / 22 (13.64%)	1 / 22 (4.55%)	
occurrences (all)	3	1	

Musculoskeletal and connective tissue disorders

Arthritis

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Back pain

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Herniated disc (recurrent)

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Infections and infestations

Cold

subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
occurrences (all)	2	1	

Fungal infection vagina

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

Metabolism and nutrition disorders

Cramps in the lower leg with lactic acidosis

subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	

Excessive thirst

subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	

hypercalcemia of unknown origin

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences (all)	1	0
increased blood sugar level		
subjects affected / exposed	1 / 22 (4.55%)	8 / 22 (36.36%)
occurrences (all)	2	18
lowered blood glucose level		
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)
occurrences (all)	5	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2017	Additional echocardiography at visit 3 & 4, addition of liver ultrasonography, 24 h blood pressure and 24 h collected urine measurement already performed at screening instead of baseline and omitted at visit 4
02 March 2018	Extension of the recruitment for 12 months

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported