Clinical trial results:
Does Dapaglifozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes?

Summary

EudraCT number	2016-000715-33
Trial protocol	GB
Global end of trial date	15 March 2019

Results information

Result version number	v1 (current)
This version publication date	03 March 2020
First version publication date	03 March 2020

Trial information

Trial identification

Sponsor protocol code	2015DM07

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Dundee
Sponsor organisation address	Ninewells Hospital , Dundee, United Kingdom, DD1 9SY
Public contact	Chim , University of Dundee, +44 01382 383013, c.c.lang@dundee.ac.uk
Scientific contact	Lang, University of Dundee, +44 01382 383013, c.c.lang@dundee.ac.uk

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	31 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2019
Global end of trial reached?	Yes
Global end of trial date	15 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To see if Dapagliflozin reduces left ventricular mass more than placebo in participants with type 2 diabetes and left ventricular hypertrophy

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 66
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	32
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place from February 2017 to May 2018

Pre-assignment

Screening details:

1541 invitation letters were sent. Overall 473 (31%) replied that they were interested. 153 were excluded from invitation if eligibility criteria were not met. A total of 320 participants were screened from February 2017 to May 2018. Out of the 320 patients screened 254 were excluded and 66 were recruited

Period 1

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

Blinding implementation details:

Participants were randomised to receive either dapagliflozin (10mg) or placebo in a double blind, randomised fashion. Trial medications were produced and packaged by Astra Zeneca but labelling of the packages were done by Tayside Pharmaceuticals. Randomisation was via TRuST, a GCP compliant web-based system, run by the Tayside Clinical Trials Unit (TCTU), to preserve allocation concealment

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapaglilflozin

Arm description:

Treatment arm which received dapagliflozin

Arm type	Active comparator
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg Once daily orally for 12 months

Arm title	Placebo

Arm description:

Participants which received placebo

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 placebo tablet daily orally

Number of subjects in period 1	Dapaglilflozin	Placebo
Started	32	34
Completed	29	33
Not completed	3	1
Adverse event, non-fatal	1	1
Unable to get holiday insurance	1	-
Claustrophobia	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	34	34	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	28	28	
Male	38	38	

End points

End points reporting groups	
Reporting group title	Dapaglilflozin
Reporting group description: Treatment arm which received dapagliflozin	
Reporting group title	Placebo
Reporting group description: Participants which received placebo	

Primary: Left ventricular mass change	
End point title	Left ventricular mass change
End point description: Change in Left ventricular mass measured by Cardiac MRI	
End point type	Primary
End point timeframe: 12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Grams				
arithmetic mean (standard deviation)	-3.95 (± 4.85)	-1.13 (± 4.55)		

Statistical analyses

Statistical analysis title	LVM change difference
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.018 [1]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.13
upper limit	-0.51
Variability estimate	Standard deviation

Notes:
[1] - Significant result

Secondary: Left ventricular mass change indexed to body surface area

End point title	Left ventricular mass change indexed to body surface area

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: g/m2				
arithmetic mean (standard deviation)	-0.58 (± 2.29)	-0.38 (± 1.79)		

Statistical analyses

Statistical analysis title	LVM indexed to BSA change difference

Statistical analysis description:
Independent T -test

Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.691 [3]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	0.8
Variability estimate	Standard deviation

Notes:
[2] - Intention to treat
[3] - Non-Significant difference

Secondary: Left ventricular ejection fraction change

End point title	Left ventricular ejection fraction change

End point description:
Change in left ventricular ejection fraction as measured by cardiac MRI

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Percentage				
arithmetic mean (standard deviation)	1.45 (± 4.08)	0.66 (± 3.76)		

Statistical analyses

Statistical analysis title	Left Ventricular ejection fraction change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.415
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	2.72
Variability estimate	Standard deviation

Notes:
[4] - Intention to treat

Secondary: End Diastolic Volume

End point title	End Diastolic Volume
End point description:	
Change in EDV as measured by cardiac MRI	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mls				
arithmetic mean (standard deviation)	-0.15 (± 11.59)	1.44 (± 10.62)		

Statistical analyses

Statistical analysis title	End Diastolic Volume Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.562 [5]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.06
upper limit	3.97
Variability estimate	Standard deviation

Notes:
[5] - Not -signficant

Secondary: End Systolic Volume

End point title	End Systolic Volume

End point description:
Change in end systolic volume as measured by cardiac MRI

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mls				
arithmetic mean (standard deviation)	-1.86 (± 4.83)	-0.74 (± 4.81)		

Statistical analyses

Statistical analysis title	End Systolic Volume
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.348 [6]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	1.25
Variability estimate	Standard deviation

Notes:

[6] - Not significant

Secondary: Stoke volume difference	
End point title	Stoke volume difference
End point description:	
Change in stroke volume as measured by cardiac MRI	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mls				
arithmetic mean (standard deviation)	1.71 (± 11.18)	2.18 (± 10.45)		

Statistical analyses

Statistical analysis title	Stroke volume change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [7]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.79
upper limit	4.85
Variability estimate	Standard deviation

Notes:
[7] - Not significant

Secondary: Cardiac Output

End point title	Cardiac Output

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mls/min				
arithmetic mean (standard deviation)	244.75 (± 1155.82)	12.91 (± 865.14)		

Statistical analyses

Statistical analysis title	Cardiac Output change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307 [8]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-257.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-757.75
upper limit	242.43
Variability estimate	Standard deviation

Notes:
[8] - Not -significant

Secondary: Left atrial volume

End point title	Left atrial volume
End point description:	
Change in left atrial volume as measured by cardiac MRI	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mls				
arithmetic mean (standard deviation)	-3.09 (± 10.12)	-1.51 (± 8.81)		

Statistical analyses

Statistical analysis title	Left atrial volume change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.501 [9]
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	-1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.24
upper limit	3.08
Variability estimate	Standard deviation

Notes:
[9] - Not-significant

Secondary: 24 Hour systolic blood pressure

End point title	24 Hour systolic blood pressure
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: mmHg				
arithmetic mean (standard deviation)	-2.78 (± 5.94)	0.85 (± 5.40)		

Statistical analyses

Statistical analysis title	24 hour blood pressure change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.012 [11]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.44
upper limit	-0.82
Variability estimate	Standard deviation

Notes:
[10] - Intention to treat analysis
[11] - Significant

Secondary: 24 hour diastolic blood pressure

End point title	24 hour diastolic blood pressure

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: mmHg				
arithmetic mean (standard deviation)	-0.94 (± 3.98)	0.06 (± 4.87)		

Statistical analyses

Statistical analysis title	24 hour diastolic blood pressure change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.37 [13]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.21
Variability estimate	Standard deviation

Notes:

[12] - Intention to treat analysis

[13] - Non-significant

Secondary: Daytime systolic blood pressure

End point title	Daytime systolic blood pressure

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: mmHg				
arithmetic mean (standard deviation)	-2.47 (± 6.56)	0.55 (± 6.45)		

Statistical analyses

Statistical analysis title	Daytime systolic blood pressure change

Statistical analysis description:

Intention to treat

Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066 [14]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.24
upper limit	0.21
Variability estimate	Standard deviation

Notes:
[14] - Non-significant

Secondary: Daytime diastolic blood pressure

End point title	Daytime diastolic blood pressure

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: mmHg				
arithmetic mean (standard deviation)	-1.03 (± 5.18)	0.24 (± 5.80)		

Statistical analyses

Statistical analysis title	Daytime diastolic blood pressure change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.355
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	1.46
Variability estimate	Standard deviation

Notes:
[15] - Intention to treat

Secondary: Nocturnal systolic blood pressure

End point title	Nocturnal systolic blood pressure

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: mmHg				
arithmetic mean (standard deviation)	-3.47 (± 7.54)	0.91 (± 6.70)		

Statistical analyses

Statistical analysis title	Nocturnal systolic blood pressure change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.017 [17]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-4.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.94
upper limit	-0.81
Variability estimate	Standard deviation

Notes:
[16] - Intention to treat
[17] - Significant

Secondary: Nocturnal diastolic blood pressure

End point title	Nocturnal diastolic blood pressure

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: mmHg				
arithmetic mean (standard deviation)	-2.25 (± 5.90)	0.16 (± 4.14)		

Statistical analyses

Statistical analysis title	Nocturnal diastolic blood pressure change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.063
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.95
upper limit	0.14
Variability estimate	Standard deviation

Notes:
[18] - Intention to treat

Secondary: Office systolic blood pressure

End point title	Office systolic blood pressure

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmHg				
arithmetic mean (standard deviation)	-5.28 (± 8.63)	-1.79 (± 7.26)		

Statistical analyses

Statistical analysis title	Office systolic blood pressure change
Statistical analysis description: Intention to treat analysis	
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08 [19]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	0.43
Variability estimate	Standard deviation

Notes:
[19] - Not significant

Secondary: Office diastolic blood pressure	
End point title	Office diastolic blood pressure
End point description:	
End point type	Secondary
End point timeframe: 12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmHg				
arithmetic mean (standard deviation)	-2.97 (± 5.62)	-2.24 (± 7.48)		

Statistical analyses

Statistical analysis title	Office diastolic blood pressure change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.656 [21]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	2.54
Variability estimate	Standard deviation

Notes:
[20] - Intention to treat analysis
[21] - Non-significant

Secondary: Visceral adipose tissue volume

End point title	Visceral adipose tissue volume

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	34		
Units: cm3				
arithmetic mean (standard deviation)	-565.17 (± 691.27)	114.22 (± 593.69)		

Statistical analyses

Statistical analysis title	Visceral adipose tissue volume change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-679.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-998
upper limit	-360.8
Variability estimate	Standard deviation

Notes:
[22] - Intention to treat analysis

Secondary: Subcutaneous adipose tissue volume

End point title	Subcutaneous adipose tissue volume
End point description:	

End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: cm3				
arithmetic mean (standard deviation)	-720.84 (± 687.83)	-111.08 (± 643.42)		

Statistical analyses

Statistical analysis title	Subcutaneous adipose tissue volume change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-609.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-948.13
upper limit	-271.28
Variability estimate	Standard deviation

Secondary: Weight

End point title	Weight
End point description:	

End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Kg				
arithmetic mean (standard deviation)	-4.27 (± 2.50)	-0.50 (± 2.19)		

Statistical analyses

Statistical analysis title	Weight Change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.92
upper limit	-2.61
Variability estimate	Standard deviation

Notes:
[23] - Intention to Treat

Secondary: BMI

End point title	BMI

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Kg/m2				
arithmetic mean (standard deviation)	-1.53 (± 0.93)	-0.17 (± 0.74)		

Statistical analyses

Statistical analysis title	BMI Change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	-0.94
Variability estimate	Standard deviation

Notes:

[24] - Intention to treat analysis

Secondary: Waist Circumference	
End point title	Waist Circumference
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: cm				
arithmetic mean (standard deviation)	-3.23 (± 2.23)	-1.39 (± 2.18)		

Statistical analyses

Statistical analysis title	Waist Circumference Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.001 [26]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	-0.75
Variability estimate	Standard deviation

Notes:
[25] - Intention to treat analysis
[26] - Significant

Secondary: Hip Circumference

End point title	Hip Circumference

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: cm				
arithmetic mean (standard deviation)	-3.39 (± 2.11)	-1.33 (± 2.21)		

Statistical analyses

Statistical analysis title	Hip Circumference Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.001 [28]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	-1
Variability estimate	Standard deviation

Notes:
[27] - Intention to treat
[28] - Significant

Secondary: Deceleration time

End point title	Deceleration time

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: ms				
arithmetic mean (standard deviation)	-8.47 (± 57.34)	4.18 (± 44.90)		

Statistical analyses

Statistical analysis title	Deceleration time change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.321
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-12.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.89
upper limit	12.6
Variability estimate	Standard deviation

Notes:

[29] - Intention to treat analysis

Secondary: Early lateral annular tissue doppler velocity

End point title	Early lateral annular tissue doppler velocity

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: cm/s				
arithmetic mean (standard deviation)	0.74 (± 2.37)	0.49 (± 1.80)		

Statistical analyses

Statistical analysis title	Early lateral annular tissue doppler velocity
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.635
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	1.28
Variability estimate	Standard deviation

Notes:
[30] - Intention to treat analysis

Secondary: Early septal annular tissue doppler velocity

End point title	Early septal annular tissue doppler velocity

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: cm/s				
arithmetic mean (standard deviation)	0.56 (± 2.22)	0.26 (± 1.36)		

Statistical analyses

Statistical analysis title	Early septall annular tissue doppler velocity
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.503
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.2
Variability estimate	Standard deviation

Secondary: Global longitudinal strain	
End point title	Global longitudinal strain
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: percentage				
arithmetic mean (standard deviation)	-1.64 (± 2.51)	-0.21 (± 1.75)		

Statistical analyses

Statistical analysis title	Global longitudinal strain
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.024
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.67
upper limit	-0.19
Variability estimate	Standard deviation

Notes:
[31] - Intention to treat analysis

Secondary: E/A Ratio

End point title	E/A Ratio

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: ratio				
median (inter-quartile range (Q1-Q3))	0.00 (-0.20 to 0.20)	0.00 (-0.20 to 0.20)		

Statistical analyses

Statistical analysis title	E/A Ratio change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.587
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.14
Variability estimate	Standard deviation

Notes:
[32] - Intention to treat analysis

Secondary: E to e ratio

End point title	E to e ratio

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: ratio				
median (inter-quartile range (Q1-Q3))	0.00 (-2.00 to 2.00)	0.10 (-0.4 to 0.20)		

Statistical analyses

Statistical analysis title	E/e ratio change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.621
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	1.1
Variability estimate	Standard deviation

Notes:

[33] - Intention to treat analysis

Secondary: Haemoglobin

End point title	Haemoglobin

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: g/l				
arithmetic mean (standard deviation)	7.00 (± 11.75)	-2.00 (± 5.00)		

Statistical analyses

Statistical analysis title	Haemoglobin change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	9.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.85
upper limit	13.18
Variability estimate	Standard deviation

Notes:
[34] - Intention to treat

Secondary: Haematocrit

End point title	Haematocrit

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Percentage				
arithmetic mean (standard deviation)	2.60 (± 0.02)	0.30 (± 0.02)		

Statistical analyses

Statistical analysis title	Haematocrit change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.84
upper limit	3.96
Variability estimate	Standard deviation

Notes:
[35] - Intention to treat analysis

Secondary: Creatinine	
End point title	Creatinine
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: umol/L				
arithmetic mean (standard deviation)	1.34 (± 5.89)	-0.91 (± 5.83)		

Statistical analyses

Statistical analysis title	Creatinine Change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.123
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	5.14
Variability estimate	Standard deviation

Notes:
[36] - Intention to treat analysis

Secondary: Estimated GFR

End point title	Estimated GFR

End point description:

End point type	Secondary

End point timeframe:
12 Months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: ml/min/1.732				
arithmetic mean (standard deviation)	-1.16 (± 10.48)	1.59 (± 7.19)		

Statistical analyses

Statistical analysis title	Estimated GFR Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.217
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.14
upper limit	1.65
Variability estimate	Standard deviation

Notes:
[37] - Intention to treat analysis

Secondary: Fasting Glucose

End point title	Fasting Glucose

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmol/L				
arithmetic mean (standard deviation)	-1.06 (± 2.08)	0.62 (± 2.11)		

Statistical analyses

Statistical analysis title	Fasting Glucose Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	-0.65
Variability estimate	Standard deviation

Secondary: HbA1c

End point title	HbA1c

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmol/mol				
arithmetic mean (standard deviation)	-6.28 (± 8.25)	-0.79 (± 10.89)		

Statistical analyses

Statistical analysis title	HbA1c
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.025
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.26
upper limit	-0.71
Variability estimate	Standard deviation

Notes:

[38] - Intention to treat analysis

Secondary: LDL Cholesterol

End point title	LDL Cholesterol

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmol/mol				
arithmetic mean (standard deviation)	-0.14 (± 0.31)	-0.08 (± 0.45)		

Statistical analyses

Statistical analysis title	LDL Cholesterol change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.522
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.13
Variability estimate	Standard deviation

Secondary: Total cholesterol	
End point title	Total cholesterol
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmol/mol				
median (inter-quartile range (Q1-Q3))	-0.10 (-0.30 to 0.03)	-0.17 (-0.38 to 0.11)		

Statistical analyses

Statistical analysis title	Total cholesterol
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.995
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	-0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.15
Variability estimate	Standard deviation

Notes:
[39] - Intention to treat analysis

Secondary: HDL Cholesterol

End point title	HDL Cholesterol

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmol/l				
median (inter-quartile range (Q1-Q3))	0.06 (-0.02 to 0.17)	0.00 (-0.04 to 0.06)		

Statistical analyses

Statistical analysis title	HDL Cholesterol
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.031
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.15
Variability estimate	Standard deviation

Notes:
[40] - Intention to treat analysis

Secondary: Total Cholesterol to HDL ratio

End point title	Total Cholesterol to HDL ratio

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Ratio				
median (inter-quartile range (Q1-Q3))	-0.20 (-0.50 to -0.03)	-0.10 (-0.30 to 0.13)		

Statistical analyses

Statistical analysis title	Total cholesterol to HDL ratio change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.085
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.01
Variability estimate	Standard deviation

Notes:

[41] - Intention to treat analysis

Secondary: Triglycerides

End point title	Triglycerides

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: mmol/l				
median (inter-quartile range (Q1-Q3))	-0.11 (-0.31 to 0.00)	0.01 (-0.26 to 0.35)		

Statistical analyses

Statistical analysis title	Triglycerides Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.064
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.08
Variability estimate	Standard deviation

Notes:

[42] - Intention to Treat analysis

Secondary: NTproBNP

End point title	NTproBNP

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	7.14 (-41.25 to 97.44)	40.19 (-68.69 to 150.78)		

Statistical analyses

Statistical analysis title	NTproBNP change
Comparison groups	Placebo v Dapaglilflozin
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.551
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-103.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-326.9
upper limit	119.54
Variability estimate	Standard deviation

Notes:

[43] - Intention to treat analysis

Secondary: Leptin	
End point title	Leptin
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	-447.55 (-4122.50 to 1170.00)	477.60 (-3200.00 to 3120.00)		

Statistical analyses

Statistical analysis title	Leptin Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.256
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-2931.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6901.46
upper limit	1038.07
Variability estimate	Standard deviation

Notes:
[44] - Intention to treat analysis

Secondary: Myeloperoxidase

End point title	Myeloperoxidase

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	0.00 (-73.56 to 33.48)	-36.49 (-36.49 to 7.28)		

Statistical analyses

Statistical analysis title	Myeloperoxidase Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	23.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.05
upper limit	77.08
Variability estimate	Standard deviation

Secondary: NT pro collagen

End point title	NT pro collagen

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: ng/ml				
arithmetic mean (standard deviation)	-0.44 (± 5.06)	-0.10 (± 4.24)		

Statistical analyses

Statistical analysis title	NT pro collagen change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.653
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	1.29
Variability estimate	Standard deviation

Notes:

[45] - Intention to treat analysis

Secondary: hsCRP

End point title	hsCRP

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: ng/l				
median (inter-quartile range (Q1-Q3))	-163.73 (-991.86 to 48.90)	66.73 (-469.26 to 789.10)		

Statistical analyses

Statistical analysis title	hs CRP Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.049
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-1296.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2650.59
upper limit	-31.5
Variability estimate	Standard deviation

Notes:

[46] - Intention to treat analysis

Secondary: Fasting Insulin

End point title	Fasting Insulin

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: uU/ml				
median (inter-quartile range (Q1-Q3))	-2.34 (-5.46 to 0.13)	-0.58 (-3.43 to 3.71)		

Statistical analyses

Statistical analysis title	Fasting Insulin Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.97
upper limit	-0.26
Variability estimate	Standard deviation

Secondary: HOMA-IR

End point title	HOMA-IR
End point description:	
End point type	Secondary
End point timeframe:	
12 Months	

End point values	Dapaglilflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: BLANK				
median (inter-quartile range (Q1-Q3))	-1.29 (-2.34 to 0.02)	-0.22 (-1.27 to 1.96)		

Statistical analyses

Statistical analysis title	HOMA-IR Change
Comparison groups	Dapaglilflozin v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.017
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-2.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.47
upper limit	-0.65
Variability estimate	Standard deviation

Notes:

[47] - Intention to treat analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from February 2017 to May 2019

Adverse event reporting additional description:

Adverse events were assessed at every trial visit. Participants were also encouraged to contact myself the Principal investigator for the trial if adverse events developed.
All reported adverse events (AEs) were recorded in detail on an adverse event CRF page.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Adverse Events Dapagliflozin

Reporting group description:

Adverse events affecting the dapaglilfozin arm

Reporting group title	Adverse Events Placebo

Reporting group description:

Adverse events reported in the placebo arm

Serious adverse events	Adverse Events Dapagliflozin	Adverse Events Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	3 / 34 (8.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Jaw Fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Adverse Events Dapagliflozin	Adverse Events Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 32 (75.00%)	30 / 34 (88.24%)	
Vascular disorders			
Postural Hypotension			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Night sweats			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Anorexia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 32 (9.38%)	2 / 34 (5.88%)	
occurrences (all)	3	2	
Cold			

subjects affected / exposed	4 / 32 (12.50%)	5 / 34 (14.71%)	
occurrences (all)	4	5	
Lower respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	4 / 34 (11.76%)	
occurrences (all)	1	4	
Flu			
subjects affected / exposed	3 / 32 (9.38%)	3 / 34 (8.82%)	
occurrences (all)	3	3	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Investigations			
Elevated Liver Enzymes			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Chest Pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Headache			

subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Vertigo			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Earache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 32 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Stomach Pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	3 / 32 (9.38%)	1 / 34 (2.94%)	
occurrences (all)	4	2	
Indigestion			

subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Tooth Abscess			
subjects affected / exposed	1 / 32 (3.13%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Abdominal hernia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Halitosis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	8 / 32 (25.00%)	7 / 34 (20.59%)	
occurrences (all)	8	7	
Renal failure	Additional description: Drop in GFR temporary in all cases		
subjects affected / exposed	2 / 32 (6.25%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Urinary Frequency			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 32 (6.25%)	3 / 34 (8.82%)	
occurrences (all)	2	3	
Supraspinatus Tendonitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Fracture			

subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Trigger finger			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Neck Pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Knee Pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Cramps			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Achilles Tendonitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Muscle Aches			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 32 (3.13%)	4 / 34 (11.76%)	
occurrences (all)	1	6	
Tinea Pedis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Thrush			
subjects affected / exposed	12 / 32 (37.50%)	2 / 34 (5.88%)	
occurrences (all)	12	2	
Ear infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	

Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	7 / 32 (21.88%)	3 / 34 (8.82%)	
occurrences (all)	22	7	
Iron deficiency anaemia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Thirst			
subjects affected / exposed	1 / 32 (3.13%)	3 / 34 (8.82%)	
occurrences (all)	1	3	
Hyponatraemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2016	AM01 Response to MHRA following initial submission Exclusion criteria updated to say that patients with electrolyte disturbance would be excluded. Patients with a history of DKA to be excluded. Asked to clarify women of child bearing potential therefore added to protocol that they would be defined as premenopausal women who have not been surgically sterilised or had a hysterectomy, bilateral salpingoophorectomy or bilateral oophorectomy. Women over 45 years old, who had no had a menstrual period for at least 12 months without an alternative cause were considered as post menopausal Added that women of child bearing age would have a urine pregnancy test pre starting the study and this would be repeated and documented every 4 weeks throughout their participation in the trial Asked to add that if a participant was commenced on loop diuretics would be discontinued from the trial
02 June 2017	AMO2 Changed lower limit of HbA1c cut off for inclusion from 53mmol/mol to 48mmol/mol Changed echocardiographic inclusion criteria to include LVH indexed to Height2.7 in addition to BSA Changed age cut off for inclusion from 75 to 80 years of age Increased weight cut off in inclusion criteria to 150kg from 120kg Added the use of the Scottish primary care research network to recruit participants Extended recruitment to Fife Added that participants would undergo an echocardiogram at the end of the study to allow the comparison of diastolic parameters and longitudinal analysis with baseline echocardiogram Allowed the ability to repeat Sodium and Potassium blood tests if tests at a review visit were abnormal to avoid unnecessary withdrawal.
12 December 2017	AMO3 Change of CI from Prof Allan Struthers to Prof Chim Lang due to Prof Struthers retiring Made a change to allow any patients who dropped out whilst recruitment was still underway to be replaced Change the GFR cut off in inclusion criteria from <60 TO < 45ml/min Following discussion with the MHRA clarified that adverse reactions with Dapagliflozin did not need to be reported via the yellow card scheme
03 September 2018	Non substantial amendment AMO4 Reduced follow up from 12months to a minimum of 10 months In the previous amendment we were allowed to replace any withdrawals during the recruitment period. Protocol therefore changed from 64 participants to 66 as 66 had been recruited at the completion of recruitment
31 January 2019	AM05 Non substantial amendment Due to funding we elected to only analyse biomarkers at the beginning and end of the study Post reading the up to date literature we decided to analyse - Myeloperoxidase, Leptin, hsCRP, NT pro BNP, procollagenIII. This was therefore added to the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported