Clinical trial results:
Research into the Effect Of SGLT2 inhibition on left ventricular Remodelling in patients with heart failure and diabetes Mellitus

Summary

EudraCT number	2014-002742-42
Trial protocol	GB
Global end of trial date	11 August 2017

Results information

Result version number	v1 (current)
This version publication date	14 July 2019
First version publication date	14 July 2019

Trial information

Trial identification

Sponsor protocol code	2013DM19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02397421
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor reference: 2013DM19

Notes:

Sponsors

Sponsor organisation name	Tayside Clinical Trials Unit
Sponsor organisation address	George Pirie Way, Dundee, United Kingdom, DD1 9SY
Public contact	Dr Fiona Hoagrth, University of Dundee, Tayside Clinical Trials Unit, +44 01382383233, f.j.hogarth@dundee.ac.uk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2017
Global end of trial reached?	Yes
Global end of trial date	11 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective will be to see if Dapagliflozin can change the harmful effect of scarring in the left ventricle in the heart of type 2 diabetic patients who have mild heart failure.

This will be done by measuring the size of the left side of the heart muscle with an MRI scan before and after one years of treatment with dapagliflozin or placebo.

Protection of trial subjects:

Approval of trial methods by East of Scotland Ethics Committee
No further specific protection methods required

Background therapy:

Various medications for host of co-morbidities as indicated (eg Aspirin, beta-blockers, ACE-inhibitiors, mineralocorticoid receptor antagoinsts, metformin, insulin etc)

Evidence for comparator:

Comparator was standard of care

Actual start date of recruitment	15 May 2015
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	United Kingdom: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	16

From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment from May 2015 till Aug 2016
Occurred in single center: Ninewells Hospital and Medical School, Dundee, UK

Pre-assignment

Screening details:

Initial screening of e-health records: 2955
Pre screening via telephone: 265
Invited to participate: 85
Informed consent: 62
Recruited: 56

Period 1

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

Blinding implementation details:

After successful recruitment into the trial, patients were randomised to either dapagliflozin 10 mg or matching placebo in a double-blind fashion. The trial medication (dapagliflozin or placebo) was prepared, packaged and labelled by our onsite clinical trials pharmaceutical manufacturer. Randomisation was carried out by our dedicated clinical trials pharmacy using block randomisation. They used a validated randomisation program and securely backed-up both the randomisation seed and the treatmen

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm

Arm description:

Dapagliflozin 10mg OD for 1 year

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

10mg once daily at any time with or without food

Arm title	Comparator Arm

Arm description:

Comparator with placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 tablet once daily

Number of subjects in period 1	Treatment arm	Comparator Arm
Started	28	28
Completed	26	23
Not completed	2	5
Consent withdrawn by subject	1	1
Non-adverse event death	-	3
New onset of cancer	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	56	56	
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)	16	16	
From 65-84 years	40	40	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	67.1		
standard deviation	± 6.8	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	37	37	
New York Heart Association Functional Classification for Heart Failure Units: Subjects			
NYHA I	25	25	
NYHA II	24	24	
NYHA III	7	7	
Left ventricular end systolic volume Units: ml			
arithmetic mean	102.7		
standard deviation	± 50.5	-	
Left ventricular end diastolic volume Units: ml			
arithmetic mean	180.0		
standard deviation	± 61.0	-	
Weight Units: kg			
arithmetic mean	95.1		
standard deviation	± 18.6	-	
Systolic blood pressure Units: mmHg			
arithmetic mean	133.9		

standard deviation	± 17.1	-	
Diastolic blood pressure Units: mmHg			
arithmetic mean	72.7		
standard deviation	± 10.0	-	
Left ventricular ejection fraction Units: percent			
arithmetic mean	45.5		
standard deviation	± 12.0	-	
Left ventricular mass indexed Units: mg/m2			
arithmetic mean	71.5		
standard deviation	± 17.7	-	

End points

End points reporting groups	
Reporting group title	Treatment arm
Reporting group description: Dapagliflozin 10mg OD for 1 year	
Reporting group title	Comparator Arm
Reporting group description: Comparator with placebo	

Primary: Left ventricular end-systolic volume	
End point title	Left ventricular end-systolic volume
End point description: Cardiac MRI determined Left ventricular end-systolic volume	
End point type	Primary
End point timeframe: 1 year	

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: ml				
arithmetic mean (standard deviation)	90.5 (± 40.0)	87.6 (± 41.5)		

Statistical analyses

Statistical analysis title	Multivariable linear regression
Statistical analysis description: Linear regression analysis comparing final outcome variables between dapagliflozin and placebo groups, while controlling for baseline values, age, gender and renal function (ANCOVA).	
Comparison groups	Treatment arm v Comparator Arm
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	19

Variability estimate	Standard deviation

Secondary: Weight

End point title	Weight

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: kg				
arithmetic mean (standard deviation)	91.5 (± 18.9)	90.3 (± 18.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular end diastolic volume

End point title	Left ventricular end diastolic volume

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[1]	23		
Units: ml				
arithmetic mean (standard deviation)	164.4 (± 50.8)	164.3 (± 62.3)		

Notes:

[1] -

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular mass indexed

End point title	Left ventricular mass indexed

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: kg/m2				
arithmetic mean (standard deviation)	74.3 (± 21.0)	74.3 (± 18.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin

End point title	Hemoglobin

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: g/dl				
arithmetic mean (standard deviation)	14.4 (± 1.4)	13.7 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic blood pressure

End point title	Systolic blood pressure

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: mmHg				
arithmetic mean (standard deviation)	137.7 (± 17.0)	136.4 (± 24.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic blood pressure

End point title	Diastolic blood pressure

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: mmHg				
arithmetic mean (standard deviation)	73.7 (± 9.3)	80.2 (± 11.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular ejection fraction

End point title	Left ventricular ejection fraction

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Treatment arm	Comparator Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: percent				
arithmetic mean (standard deviation)	47.1 (± 11.4)	47.9 (± 10.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 1 year	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	Treatment arm
Reporting group description: Dapagliflozin 10mg OD for 1 year	
Reporting group title	Comparator Arm
Reporting group description: Comparator with placebo	

Serious adverse events	Treatment arm	Comparator Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 28 (10.71%)	10 / 28 (35.71%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			

subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Ear and labyrinth disorders			
Otitis externa bacterial			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung cancer metastatic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
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: 5 %

Non-serious adverse events	Treatment arm	Comparator Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 28 (39.29%)	14 / 28 (50.00%)	
General disorders and administration site conditions			

Dehydration			
subjects affected / exposed	3 / 28 (10.71%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 28 (10.71%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
Urinary tract infection			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Candida infection			
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	3 / 28 (10.71%)	2 / 28 (7.14%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2015	• This was made upon REC request for clarification of safety measures, withdrawal and early discontinuation of IMP. Final favorable opinion from REC was granted on 15th January 2015.
25 August 2015	• Submitted for approval on 16th June 2015, all relevant approvals were obtained by 25th August 2015. • Inclusion/exclusion criteria was altered to include patients taking sulphonylureas and to increase the maximal furosemide dose. • Secondary endpoints of the trial were amended to include measurement of urinary albumin: creatinine ratio and urinary sodium excretion. • Measurements of atrial dimensions and left ventricular remodelling index has been added to the cardiac MRI. • Assessment of fluid status using the BIA machine at every visit has been added.
15 December 2015	• Submitted for approval on 22nd October 2015, all relevant approvals were obtained by 15th December 2015. • Primary outcome measures was amended to include left ventricle volume measurement which was previously a secondary outcome measure. • The exclusion criteria has been altered to allow the concomitant use of insulin with IMP and the cut off for renal disease was lowered to 45mL/min.
01 July 2016	• Updating the PIS, informed consent form and trial protocol to reflect new MHRA advisory regarding non-hyperglycaemic ketoacidosis among patients on SGLT2-inhibitor therapy. • Addition of the University of Dundee's GO-DARTS database as a new source of recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported