



Clinical trial results:

Renal and Cardiovascular Effects of SGLT2 inhibition in combination with loop diuretics in diabetic patients with chronic heart failure.

Summary

EudraCT number	2016-003968-39
Trial protocol	GB
Global end of trial date	09 January 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	2015CA02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03226457
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Reference: 2015CA02, REC: Regional Ethics Committee Reference: 16/ES/0137

Notes:

Sponsors

Sponsor organisation name	University of Dundee & Tayside Health Board
Sponsor organisation address	George Pirie Way, Dundee, United Kingdom, DD1 9SY
Public contact	Professor Jacob George , University of Dundee & Tayside Health Board Tayside Medical Science Centre, Ninewells Hospital, 01382 383204, J.George@dundee.ac.uk
Scientific contact	Professor Jacob George , University of Dundee & Tayside Health Board Tayside Medical Science Centre, Ninewells Hospital, 01382 383204, J.George@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	01 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2019
Global end of trial reached?	Yes
Global end of trial date	09 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective will be to assess whether empagliflozin (SGLT2 Inhibitor) can augment the effects of loop diuretics in diabetic patients with mild congestive heart failure with left ventricular systolic dysfunction (LVSD), as measured by urinary volume.

Protection of trial subjects:

Participants were recruited had both Type 2 Diabetes (T2D) and Heart Failure (HF). Whilst this co-morbidity can often lead to frailty, the inclusion/exclusion criteria ensured that participants with stable T2D and HF were recruited.

Participants were eligible if they were:

- Aged 18 to 80 years with previously diagnosed Type 2 Diabetes Mellitus.
- Diagnosed with NYHA Functional class II-III HF with prior echocardiographic evidence of LVSD.
- On stable doses of furosemide, or alternative loop diuretic for at least one month.
- Type 2 Diabetes
- eGFR $\geq$ 45 ml/min.
- Had stable HF symptoms for at least three months prior to consent
- On stable HF therapy for at least three months prior to consent
- Had not been hospitalised for HF for at least three months prior to consent.
- Women of childbearing potential* (WoCBP) agreed to take precautions to avoid pregnancy throughout the trial and for 4 weeks after intake of the last dose.

Participants will be excluded if they had:

- A diagnosis of chronic liver disease and/or liver enzymes that are twice the upper limit of normal
- Systolic BP of <95mmHg at screening visit.
- HbA1c < 6.0%
- Participants on thiazide diuretics.
- Participants receiving renal dialysis
- Participants who had previously had an episode of diabetic ketoacidosis.
- Participants with type 1 diabetes mellitus
- Malignancy (receiving active treatment) or other life threatening disease.
- Pregnant or lactating women
- Participants with difficulty in micturition e.g. severe prostate enlargement
- Allergy to any SGLT2 inhibitor or lactose or galactose intolerance
- Past or current treatment with any SGLT2 inhibitor
- Participants who have participated in any other clinical interventional trial of an investigational medicinal product within 30 days.
- Participants who are unable to give informed consent
- Any other reason considered by the physician to be inappropriate for inclusion.

Background therapy:

Participants recruited were on HF medications (except for thiazide diuretics) and could be on T2D medications or have diet-controlled T2D.

Evidence for comparator:

The landmark EMPA-REG outcome study reported a striking 35% relative risk reduction in HF hospitalisations with empagliflozin providing supportive evidence for the beneficial effects of SGLT2 inhibition in the setting of chronic HF. The early separation curves on the Kaplan-Meier graphs and the effect on HF hospitalisations has led to the hypothesis that this outcome is seen due to a diuretic effect

of SGLT2 inhibition.

Data on the effect of SGLT2 inhibitor use with diuretics are limited, but given the relative frequency of both HF and T2D they are likely to be prescribed concurrently. The RECEDE-CHF trial sets out to explore this in more detail.

Actual start date of recruitment	30 November 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	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	5
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A high drop out rate was factored into the power calculations due to the high intensity of the patient visits. A minimum of 22 participants was required to meet the power calculations. There were no patient drop outs and 23 patients were recruited and completed participation in the trial.

Pre-assignment

Screening details:

At the screening visit, following informed consent, an initial medical history and clinical examination was performed and concomitant medication will be recorded. Participants had bloods taken for safety analysis and vital signs will be checked to confirm eligibility prior to enrolment.

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	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Participants were randomised to either empagliflozin 25mg/ placebo or placebo/empagliflozin 25 mg in a double blind fashion.

The double blind medication (empagliflozin or placebo) was prepared, packaged and labelled by Tayside Pharmaceuticals.

The Clinical Trials Pharmacy, Ninewells Hospital were provided with a copy of the randomisation allocation for the purposes of 24 hour emergency unblinding.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Placebo arm, one tablet once a day for 6 weeks

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

Dosage and administration details:

Placebo, one tablet once a day

Arm title	Empagliflozin 25 mg
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Arm description:

Empagliflozin 25 mg, one tablet once a day for 6 weeks

Arm type	Experimental
Investigational medicinal product name	Empagliflozin 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 25 mg once daily, oral administration

Number of subjects in period 1	Placebo	Empagliflozin 25 mg
Started	23	23
Completed	23	23

Baseline characteristics

Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	23	23	
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	69.8		
standard deviation	± 5.6	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	17	17	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo arm, one tablet once a day for 6 weeks	
Reporting group title	Empagliflozin 25 mg
Reporting group description: Empagliflozin 25 mg, one tablet once a day for 6 weeks	

Primary: Change in 24 hour urine volume from baseline to day 3

End point title	Change in 24 hour urine volume from baseline to day 3
End point description:	
End point type	Primary
End point timeframe: Change in 24 hour urine volume from baseline to day 3	

End point values	Placebo	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: millilitres				
least squares mean (confidence interval 95%)	-117.65 (-348.78 to 113.49)	425.16 (118.26 to 662.07)		

Statistical analyses

Statistical analysis title	Change in 24 hour urine volume from baseline to D3
Comparison groups	Placebo v Empagliflozin 25 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 ^[1]
Method	ANCOVA

Notes:

[1] - Mean difference from placebo 549.30 mls (151.42 to 947.17; 95% CI), p value < 0.004

Primary: Change in 24 hour urine volume from baseline to week 6

End point title	Change in 24 hour urine volume from baseline to week 6
End point description:	

End point type	Primary
End point timeframe:	
Change in 24 hour urine volume from baseline to week 6	

End point values	Placebo	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: millilitre(s)				
least squares mean (confidence interval 95%)	-117.65 (-348.78 to 113.49)	425.16 (188.26 to 662.07)		

Statistical analyses

Statistical analysis title	Change in 24h urinary volume from baseline to wk6
Comparison groups	Placebo v Empagliflozin 25 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change in 24 hour urinary sodium at week 6 from baseline

End point title	Change in 24 hour urinary sodium at week 6 from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Change in 24 hour urinary sodium at week 6 from baseline	

End point values	Placebo	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: millimole(s)/litre				
least squares mean (confidence interval 95%)	0.42 (-10.26 to 11.10)	-7.99 (-18.7 to 2.69)		

Statistical analyses

Statistical analysis title	Change in 24 hour urinary sodium at week 6
Comparison groups	Placebo v Empagliflozin 25 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	ANCOVA

Secondary: Change in serum creatinine at week 6 from baseline

End point title	Change in serum creatinine at week 6 from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Change in serum creatinine at week 6 from baseline	

End point values	Placebo	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: millimole(s)/litre				
least squares mean (confidence interval 95%)	-10.81 (-19.2 to -2.44)	-0.44 (-8.82 to 7.94)		

Statistical analyses

Statistical analysis title	Change in serum creatinine at week 6 from baseline
Comparison groups	Placebo v Empagliflozin 25 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.512
Method	ANCOVA

Secondary: Change in urinary Protein:Creatinine Ratio at week 6 from baseline

End point title	Change in urinary Protein:Creatinine Ratio at week 6 from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Change in urinary Protein:Creatinine Ratio at week 6 from baseline	

End point values	Placebo	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: milligram/millimol				
least squares mean (confidence interval 95%)	-3.05 (-7.05 to 0.97)	2.26 (-1.75 to 6.28)		

Statistical analyses

Statistical analysis title	Change in urine PCR from baseline to wk6
Comparison groups	Placebo v Empagliflozin 25 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.399
Method	ANCOVA

Secondary: Change in urinary Albumin:Creatinine Ratio at week 6 from baseline

End point title	Change in urinary Albumin:Creatinine Ratio at week 6 from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Change in urinary Albumin:Creatinine Ratio at week 6 from baseline	

End point values	Placebo	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: milligram/millimol				
least squares mean (confidence interval 95%)	-1.10 (-2.98 to 0.77)	1.18 (-0.69 to 3.05)		

Statistical analyses

Statistical analysis title	Change in uACR from baseline to week 6
Comparison groups	Placebo v Empagliflozin 25 mg

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.543
Method	ANCOVA

Secondary: Change in cystatin C from baseline to week 6

End point title	Change in cystatin C from baseline to week 6
End point description:	
End point type	Secondary
End point timeframe:	
Change in cystatin C from baseline to week 6	

End point values	Placebo	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: nanogram/millilitre				
least squares mean (confidence interval 95%)	22.50 (-91.52 to 136.52)	31.35 (-80.07 to 142.75)		

Statistical analyses

Statistical analysis title	Change in cystatin C from baseline to week 6
Comparison groups	Placebo v Empagliflozin 25 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.99
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to the last patient visit (visit 10), which was 4 weeks post discontinuation of investigational medicinal product (both treatment arms and last arm being either empagliflozin 25 mg od or placebo).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo arm, one tablet once a day for 6 weeks

Reporting group title	Empagliflozin 25 mg
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Reporting group description:

Empagliflozin 25 mg, one tablet once a day for 6 weeks

Serious adverse events	Placebo	Empagliflozin 25 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 23 (13.04%)	2 / 23 (8.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive	Additional description: 2 x cases of Cardiac Failure (congestive), 1 on placebo (after washout period following treatment of empagliflozin) and 1 on discontinuation of empagliflozin.		
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal Haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Delerium	Additional description: In relation to sepsis caused by cellulitis		
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Empagliflozin 25 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 23 (39.13%)	13 / 23 (56.52%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Vascular disorders			
hypotension			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

Dizziness subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 23 (4.35%) 1	
General disorders and administration site conditions Thirst subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 23 (4.35%) 1	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 0 / 23 (0.00%) 0	2 / 23 (8.70%) 2 1 / 23 (4.35%) 1	
Respiratory, thoracic and mediastinal disorders Lower respiratory tract infection subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1 1 / 23 (4.35%) 2	1 / 23 (4.35%) 1 0 / 23 (0.00%) 0	
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all) Dysuria subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 1 / 23 (4.35%) 1	2 / 23 (8.70%) 3 1 / 23 (4.35%) 1 0 / 23 (0.00%) 0	
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 23 (4.35%) 1	
Infections and infestations			

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	3 / 23 (13.04%) 3	
Balanitis candida subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 23 (4.35%) 1	
Sinusitis subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 23 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 23 (0.00%) 0	
Metabolism and nutrition disorders			
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 23 (0.00%) 0	
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 23 (4.35%) 2	
Gout subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	2 / 23 (8.70%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2018	Participant selection and enrolment: the addition of the Scottish Diabetes Research Network including GoDARTS database. Inclusion criteria was changed from HbA1c in the last 3 months of 6.5% < and <10.0%, to exclusion criteria of HbA1c < 6.0%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29042392>