Clinical trial results:
Effect of SGLT2 inhibition on coronary microvascular function in type 2 diabetes

Summary

EudraCT number	2017-000240-17
Trial protocol	DK
Global end of trial date	18 December 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2020
First version publication date	18 December 2020

Trial information

Trial identification

Sponsor protocol code	ESTIMATE

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bispebjerg University Hospital
Sponsor organisation address	Bispebjerg Bakke 23, København NV, Denmark, 2400
Public contact	Eva Prescott, Bispebjerg University Hospital, 27201195 27201195, hannah.elena.suhrs@regionh.dk
Scientific contact	Eva Prescott, Bispebjerg University Hospital, 27201195 27201195, hannah.elena.suhrs@regionh.dk

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	30 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2018
Global end of trial reached?	Yes
Global end of trial date	18 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to evaluate the effect of treatment with SGLT2 inhibitors on the coronary microvasculature in patients with type 2 diabetes mellitus

Protection of trial subjects:

none

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	12
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We included 26 participants between 21-06-2017 and 15-06-2018. Patient were followed for diabetes at the outpatient clinic at Bispebjerg University Hospital, Copenhagen, Denmark.

Pre-assignment

Screening details:

We screened hospital records of 1196 patients. A letter of invitation was sent to 322 patients who passed the initial pre-screening and 47 passed the second pre-screening after contact was established by phone.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Empagliflozine

Arm description:

12 weeks treatment with empagliflozine

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

Dosage and administration details:

25 mg empagliflozine daily for 12 weeks

Arm title	Placebo

Arm description:

12 weeks treatment with placebo

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

Dosage and administration details:

1 tablet daily for 12 weeks

Number of subjects in period 1	Empagliflozine	Placebo
Started	26	26
Completed	19	19
Not completed	7	7
Physician decision	2	2
reason unrelated to study	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Intervention (overall)
Reporting group description:	
As the study was designes as a cross-over study, the same subjects participated in period 1 and period 2, receiving either active treatment or placebo.	

Reporting group values	Intervention (overall)	Total	
Number of subjects	26	26	
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	60.5		
full range (min-max)	42 to 73	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	17	17	
coronary flow velocity reserve			
Units: ratio			
arithmetic mean	2.60		
standard deviation	± 0.56	-	

End points

End points reporting groups

Reporting group title	Empagliflozine
Reporting group description:	
12 weeks treatment with empagliflozine	
Reporting group title	Placebo
Reporting group description:	
12 weeks treatment with placebo	

Primary: change in coronary flow velocity reserve

End point title	change in coronary flow velocity reserve
End point description:	
Coronary flow velocity reserve is the ratio of the coronary flow velocity at hyperemia to rest. Change in coronary flow velocity reserve was the primary endpoint.	
End point type	Primary
End point timeframe:	
Coronary flow velocity reserve was measured before and after 12 weeks treatment with empagliflozine and before and after 12 weeks treatment with placebo.Change in coronary flow velocity reserve was the primary endpoint.	

End point values	Empagliflozine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: ratio				
arithmetic mean (standard deviation)	-0.16 (± 0.58)	0.18 (± 0.60)		

Statistical analyses

Statistical analysis title	two-sample t-test
Statistical analysis description:	
Data was analyzed as two-sample t-test comparing changes within and between the empagliflozin treatment group and the placebo group after ensuring there was no carry over, sequence or period effect. Carry over effects were measured using the pkcross command in Stata 13.1 for cross-over design studies. Paired two-sample t-test was used for within allocation comparisons whereas unpaired two-sample t-test was used for between treatment allocation comparisons.	
Comparison groups	Empagliflozine v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported at a scheduled clinical visit 1-3 weeks after initiating treatment and thereafter at a scheduled phone call approximately 14 days later. When needed extra phonecalls were planned.

Adverse event reporting additional description:

Adverse event were registered by regular clinical visits and phone calls. Participants had a direct number to study staff on working days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Empagliflozine

Reporting group description:

12 weeks treatment with empagliflozine

Reporting group title	Placebo

Reporting group description:

12 weeks treatment with placebo

Serious adverse events	Empagliflozine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Empagliflozine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 26 (30.77%)	5 / 26 (19.23%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paget's disease of nipple			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			

subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
drop in renal function			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Muscle discomfort			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Skin infection			
subjects affected / exposed	4 / 26 (15.38%)	2 / 26 (7.69%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported