Clinical trial results:
Effects of SGLT-2 Inhibitor on Myocardial Perfusion, Function and Metabolism in Type 2 DM Patients at high cardiovascular risk: The SIMPle Randomized Clinical Trial

Summary

EudraCT number	2016-003743-10
Trial protocol	DK
Global end of trial date	22 May 2020

Results information

Result version number	v1 (current)
This version publication date	07 November 2021
First version publication date	07 November 2021

Trial information

Trial identification

Sponsor protocol code	2016-779

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03151343
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev & Gentofte Hospital
Sponsor organisation address	Herlev Ringvej 75, Herlev, Denmark, 2730
Public contact	Center for Endokrinologi, Herlev og Gentofte Hospital, mikkel.juergens.01@regionh.dk
Scientific contact	Center for Endokrinologi, Herlev & Gentofte Hospital, mikkel.juergens.01@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	28 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 May 2020
Global end of trial reached?	Yes
Global end of trial date	22 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine the mechanism behind the cardioprotective effects of the SGLT-2 inhibitor empagliflozine in a population of type 2 diabetics at high cardiovascular risk.

Protection of trial subjects:

Schedueled safety assessments, in-person as well as by telephone. The trial was monitored by the Good Clinical Practice (GCP) unit in Copenhagen.

Background therapy: -

Evidence for comparator:

Comparator was placebo

Actual start date of recruitment	29 March 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	Denmark: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	34
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from outpatient clinics at Herlev & Gentofte Hospital and Rigshospitalet in Denmark, in the period 29 Mar 2017 to 12 Feb 2020.

Pre-assignment

Screening details:

Key inclusion criteria were a diagnosis of type 2 diabetes and established cardiovascular disease. Key exclusion criteria were eGFR ≤30 mL/min, and treatment with any SGLT2i within 1 month before study enrollment.

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:

Trial medication and randomization sequence was provided by a central pharmacy (Glostrup Apotek). Patients and investigators were blinded to group allocation for the duration of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description: -

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

Dosage and administration details:

25 mg, once daily

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

once daily

Number of subjects in period 1[1]	Active	Placebo
Started	45	45
Completed	42	36
Not completed	3	9
COVID lockdown	-	3
Adverse event, non-fatal	2	1
Claustrophobia	-	3
Technical issues	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One person was enrolled but not randomized. The person dropped out before randomization due to medical reasons.

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Active	Placebo	Total
Number of subjects	45	45	90
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	66	67	
standard deviation	± 9	± 9	-
Gender categorical Units: Subjects			
Female	11	7	18
Male	34	38	72
Myocardial Flow Reserve at baseline Units: ratio			
arithmetic mean	2.17	2.26	
standard deviation	± 0.63	± 0.67	-

End points

End points reporting groups

Reporting group title	Active
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Myocardial Flow Reserve

End point title	Myocardial Flow Reserve
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to 13 weeks	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: ratio				
arithmetic mean (confidence interval 95%)	0.01 (-0.18 to 0.21)	0.06 (-0.15 to 0.27)		

Statistical analyses

Statistical analysis title	Constrained linear mixed model
Comparison groups	Active v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.23

Notes:

[1] - Difference in change in means

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From signing the informed consent form until two weeks after the end of the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	2021-07-31
Reporting groups	
Reporting group title	Active
Reporting group description: Participants receiving active treatment	
Reporting group title	Placebo
Reporting group description: Participants receiving placebo	

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm of colon and/or rectum			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Transient ischemic attac			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low blood pressure			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
Erysipelas			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Abscess	Additional description: Right foot. Condition led to amputation of toes 1 and 2.		
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
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: 3 %

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 45 (44.44%)	9 / 45 (20.00%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Angina			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Vaginitis			
subjects affected / exposed	3 / 45 (6.67%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Renal and urinary disorders			
Increased frequency of urination			
subjects affected / exposed	14 / 45 (31.11%)	1 / 45 (2.22%)	
occurrences (all)	14	1	
Musculoskeletal and connective tissue disorders			

Low back pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 45 (4.44%) 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study had a small number of participants (90), and some data could not be obtained due to COVID restrictions

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34278803