Clinical trial results:
The Effect of Empagliflozin on Cardiac and Kidney Metabolism in Persons with Type 2 Diabetes

Summary

EudraCT number	2017-001779-22
Trial protocol	DK
Global end of trial date	19 December 2019

Results information

Result version number	v1 (current)
This version publication date	05 March 2021
First version publication date	05 March 2021
Summary attachment (see zip file)	Summary and abstract (Abstract_EMA.pdf)

Trial information

Trial identification

Sponsor protocol code	04.2017

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AUH
Sponsor organisation address	Palle Juul-Jensens blv. , Aarhus N, Denmark, 8200
Public contact	Department of Endorcrinology, Aarhus University Hospital, katrine.mj@rm.dk
Scientific contact	Department of Endorcrinology, Aarhus University Hospital, katrine.mj@rm.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	15 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2019
Global end of trial reached?	Yes
Global end of trial date	19 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Empagliflozin is a sodium–glucose cotransporter 2 (SGLT-2) inhibitor, and is used in treatment of diabetes type 2. It is previously shown that SGLT-2 inhibitors have a remarkable protective effect on the heart by reducing death caused by cardiac diseases with 38%. The reasons for these effects are still unknown, but it is known that SGLT-2 treatment increase ketogenesis. We have in a previous study found that ketone body infusion shifts cardiac metabolism towards ketone body oxidation, which possibly increases cardiac efficiency. It is also shown that SGLT-2 inhibitors have reno protective effects. The aim of this study is to examine the effects of SGLT-2 treatment by:
- Examination of substrate metabolism in heart and kidney measured by PET.
- Examination of perfusion and total energy consumption in the heart and kidney measured by PET.
- Indirect calorimetry, bloodsamples, fat- and muscle biopsies, DXA-scan, measurement of arterial stiffness and oral glucose tolerance test.

Protection of trial subjects:

Interviews about side effects to treatment
GCP guidelines has been followed

Background therapy:

Metformin

Evidence for comparator: -

Actual start date of recruitment	05 September 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: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	6
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited through advertisements in local press in the period between September 2017 - August 2019

Pre-assignment

Screening details:

- Age: 50-70 years
- Type 2 diabetes for > 1 år
- HbA1c: 48-75 mmol/mol
- Metformin treatment as only anti diabetic medicin

One-week walkout between study periods

23 volunteers were screened for inclusion. 13 participants were included. 1 withdraw consent due to claustrophobia during scans.

Period 1

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

Blinding implementation details:

Encapsulation of medicine.
Randomization and encapsulation of medicine were handled by the hospital pharmacy.
Randomization code was given after finalising data analysis

Arms

Arm title	Placebo and intervention

Arm description:

13 patients were randomized to receive placebo and Jardiance 25 mg in a crossover design. Both placebo and Jardiance were encapsulated.

Comment: I found it necessary to choose the one arm design in this report. If I selected two arms, the number of participants were doubled.

Arm type	Placebo and intervention
Investigational medicinal product name	Jardiance
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg once daily encapsulated

Number of subjects in period 1	Placebo and intervention
Started	13
Completed	12
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo and intervention in crossover

Reporting group description: -

Reporting group values	Placebo and intervention in crossover	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
Adults (18-64 years)	6	6	
From 65-84 years	7	7	
Age continuous Units: years			
arithmetic mean	62		
standard deviation	± 6	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	10	10	
Ischemic heart disease Units: Subjects			
Yes	1	1	
No	12	12	
HbA1c Units: mmol/mol			
arithmetic mean	56.7		
standard deviation	± 5.5	-	
Diabetes duration Units: years			
arithmetic mean	4.6		
standard deviation	± 3.0	-	

End points

End points reporting groups

Reporting group title	Placebo and intervention

Reporting group description:

13 patients were randomized to receive placebo and Jardiance 25 mg in a crossover design. Both placebo and Jardiance were encapsulated.

Comment: I found it necessary to choose the one arm design in this report. If I selected two arms, the number of participants were doubled.

Primary: Cardiac uptake of free fatty acids

End point title	Cardiac uptake of free fatty acids[1]

End point description:

End point type	Primary

End point timeframe:

After four weeks of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis are described in the attached article (more information)

End point values	Placebo and intervention			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: umol/100g/min				
arithmetic mean (standard deviation)				
Jardiance	7.7 (± 3.7)			
Placebo	8.2 (± 3.6)			

Attachments (see zip file)	fig2_2_columns.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Cardiac glucose uptake

End point title	Cardiac glucose uptake[2]

End point description:

End point type	Primary

End point timeframe:

After four weeks of treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis are described in the attached article (more information)

End point values	Placebo and intervention			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: umol/100g/min				
arithmetic mean (standard deviation)				
Jardiance	0.6 (± 0.6)			
Placebo	1.4 (± 0.6)			

Attachments (see zip file)	fig2_2_columns.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Cardiac oxygen consumption

End point title	Cardiac oxygen consumption[3]

End point description:

End point type	Primary

End point timeframe:

After four weeks of treatment

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis are described in the attached article (more information)

End point values	Placebo and intervention			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ml/100g/min				
arithmetic mean (standard deviation)				
Jardiance	8.8 (± 1.0)			
Placebo	9.7 (± 1.4)			

Attachments (see zip file)	fig3_2_columns.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Myocardial perfusion in rest

End point title	Myocardial perfusion in rest[4]

End point description:

End point type	Primary

End point timeframe:

After four weeks of treatment

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis are described in the attached article (more information)

End point values	Placebo and intervention			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ml/g/min				
arithmetic mean (standard deviation)				
Jardiance	0.74 (± 0.10)			
Placebo	0.85 (± 0.10)			

Attachments (see zip file)	fig3_2_columns.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 09.10.2017 - 19.12.2019	
Adverse event reporting additional description: Weekly meetings with the participants with questions regarding adverse events.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No adverse events have been reported

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33334875