Clinical trial results:
A randomized, double-blinded, placebo-controlled trial that evaluates the effect of empagliflozin on oxidative stress in patients with type 2 diabetes

Summary

EudraCT number	2016-000370-38
Trial protocol	DK
Global end of trial date	22 January 2020

Results information

Result version number	v1 (current)
This version publication date	04 February 2021
First version publication date	04 February 2021

Trial information

Trial identification

Sponsor protocol code	2016-100

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02890745
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Clinical Pharmacology, Bispebjerg-Frederiksberg Hospital - Rigshospitalet, Q7642
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark,
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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 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2020
Global end of trial reached?	Yes
Global end of trial date	22 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Urinary excretion rates of 8-oxo-7,8-dihydroguanosine (8-oxoGuo) and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) before and after treatment with empagliflozin compared to placebo treatment in addition to standard care in patients with type 2 diabetes

Protection of trial subjects:

All data was stored in accordance with the Danish Law of data protection

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 November 2016
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: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	18
From 65 to 84 years	17

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment were done in relation to patients outpatient consultation at Gentofte Hospital and Bispebjerg Hospital as well as throug advertisements at public availiable material.

Pre-assignment

Screening details:

A screening visit is performed prior to enrollment in the study to ensure elibility of study criteria with an physical examination and disease and life style history

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, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Active arm. Empagliflozin 25 mg, once daily for 14 days

Arm type	Experimental
Investigational medicinal product name	empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, tablet, oral use

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

Placebo, tablet, oral use

Number of subjects in period 1[1]	Intervention	Placebo
Started	16	15
Completed	16	15

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: A total number of 35 participants were enrolled in the study. However, 4 participants chose to withdrew before getting trial medicine, and were thus not included in the baseline information.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	31	31	
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			
Mean: 63 SD: 7			
Units: years			
arithmetic mean	63		
standard deviation	± 7	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	31	31	
Body mass index Units: kg/m^2			
arithmetic mean	30.9		
standard deviation	± 4.6	-	
HbA1c Units: mmol/mol			
arithmetic mean	56		
standard deviation	± 7	-	

End points

End points reporting groups	
Reporting group title	Intervention
Reporting group description:	
Active arm. Empagliflozin 25 mg, once daily for 14 days	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Primary: Changes in urinary excretion of 8-oxo-7,8-dihydroguanosine	
End point title	Changes in urinary excretion of 8-oxo-7,8-dihydroguanosine
End point description:	
End point type	Primary
End point timeframe:	
Changes from baseline to end of study	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: nmol/24h				
arithmetic mean (standard deviation)	-0.5 (± 7.8)	-1.8 (± 8.5)		

Statistical analyses

Statistical analysis title	Between group effects 8-oxo-7,8-dihydroguanosine
Comparison groups	Placebo v Intervention
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.66
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	4.8

Primary: Changes in urinary excretion of 8-oxo-7,8-dihydro-2'-deoxyguanosine	
End point title	Changes in urinary excretion of 8-oxo-7,8-dihydro-2'-deoxyguanosine
End point description:	
End point type	Primary
End point timeframe:	
Changes from baseline to end of study	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: nmol/24h				
arithmetic mean (standard deviation)	-1.1 (± 5.3)	-1.5 (± 6.7)		

Statistical analyses

Statistical analysis title	Between group effects 8-oxo-7,8-dihydro-2'-deoxygu
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.89
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	4.8

Secondary: Changes in plasma concentration of malondialdehyde	
End point title	Changes in plasma concentration of malondialdehyde
End point description:	
End point type	Secondary
End point timeframe:	
Changes from baseline to end of study	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: nmol/mL				
arithmetic mean (standard deviation)	-0.13 (± 0.67)	0.08 (± 0.54)		

Statistical analyses

Statistical analysis title	Between group effect malondialdehyde
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.33
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.23

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the study period (14 days) and one week afterwards	
Adverse event reporting additional description:	
Daily text messages and at the end of study. If any occured the week following the study, participants contacted the investiagator	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Intervention group
Reporting group description:	
Empagliflozin 25 mg, once daily for 14 days	
Reporting group title	Placebo
Reporting group description:	
Placebo for 14 days	

Serious adverse events	Intervention group	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (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	Intervention group	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 16 (62.50%)	6 / 15 (40.00%)	
Gastrointestinal disorders			
Increased thirst			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nausea or changed stool consistence			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			

Genital fungal infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Renal and urinary disorders Polyuria subjects affected / exposed occurrences (all)	9 / 16 (56.25%) 9	1 / 15 (6.67%) 1	
Psychiatric disorders Tired subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	2 / 15 (13.33%) 2	
Musculoskeletal and connective tissue disorders Sprained finger subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	2 / 15 (13.33%) 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 project did not include 34 participants that succesfully completed the study. 35 partipants were enrolled, however, 4 participants withdrew before starting trial medicine. Thus, 31 participants succesfully completed the study.

Notes: