EU Clinical Trials Register

Clinical trial results:
Acute effects of Sodium-glucose coTRansporter-2 inhibition on renal OxygeNation and AUTonomic function in type 1 diabetes

Summary

EudraCT number	2019-004557-92
Trial protocol	DK
Global end of trial date	23 October 2020

Results information

Result version number	v1 (current)
This version publication date	26 July 2021
First version publication date	26 July 2021

Trial information

Trial identification

Sponsor protocol code	H-19052662

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04193566
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Steno Diabetes Center Copenhagen
Sponsor organisation address	niels steensens vej 2, Gentofte, Denmark, 2820
Public contact	Jens Christian Laursen, Steno Diabetes Center Copenhagen, 0045 30913252, jens.christian.laursen.01@regionh.dk
Scientific contact	Jens Christian Laursen, Steno Diabetes Center Copenhagen, 0045 30913252, jens.christian.laursen.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	22 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 October 2020
Global end of trial reached?	Yes
Global end of trial date	23 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the study is to assess the acute effects of SGLT2 inhibition on parameters reflecting oxygenation and oxygen consumption of the human kidney in persons with type 1 diabetes.

Protection of trial subjects:

Patient risks and management of complications
The risk was considered very little with treatment with two single doses of 50 mg, even if these doses are larger than usually applied daily doses (10 mg per day), as side effects have not been observed with this or higher doses (up to 500 mg as single dose). After longer periods of using dapagliflozin, the following side-effects have been observed: Hypoglycemia, hypotension, elevated hematocrite, dyslipidemia, back pain, dizziness, skin rash, urinary tract infection, vulvovaginitis and dehydration. Very rare incidents of ketoacidosis have been observed. If the mentioned side-effects against all expectations should occur, it is common for them, that they are transient or simple to manage with standard treatment methods. Blood sampling by arterial puncture and venous puncture can cause a short pain, a small risk of hematoma and a minimal infection risk at the puncture site. Arterial puncture is also associated with a minimal risk of arteriospasm, nerve damage, fainting and thrombosis (25). The most feared complication is irreversible ischemic damage distally for the thrombosis-site. This will only happen if revascularization is not achieved before six hours after the vascular occlusion. Due to access to nearby vascular surgery, irreversible ischemic damage is not considered a realistic ultimate consequence of potentially occurring thromboses during the present study. Usually there is no discomfort associated with MRI scans. Short-term transient side-effects can be experienced: Slight increase in body temperature (< 0.6 °C), touch sensations, dizziness, nausea and taste of metal. Besides this, it can feel claustrophobic to lie in the scanner. No complications or side-effects occurred with any of the study participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2020
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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	10
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 patients with type 1 diabetes were recruited from Steno Diabetes Center Copenhagen.

Pre-assignment

Screening details:

Information about civil registration number, phone number, address, diagnosis of T1D and historic levels of urine albumin on outpatients at Steno Diabetes Center Copenhagen is provided by the treatment-responsible doctor and passed on to the study investigator for recruitment.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Dapagliflozin

Arm description:

Forxiga®, dapagliflozin 10 mg film-coated tablets. The intervention is a single dose of 50 mg.
For further information please refer to:
https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf.

Arm type	Active comparator
Investigational medicinal product name	Forxiga
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the active arm will be treated with dapagliflozin 50 mg once on site for visit 2 and once at home on the evening before visit 3.

Arm title	Placebo

Arm description:

The composition equals the composition of Forxiga® – just with the active ingredient omitted. Active drug and placebo are similar in appearance and smell.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The composition equals the composition of Forxiga® – just with the active ingredient omitted. Active drug and placebo are similar in appearance and smell.

Number of subjects in period 1	Dapagliflozin	Placebo
Started	15	15
Completed	15	15

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	58		
standard deviation	± 14	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	10	10	

End points

End points reporting groups

Reporting group title	Dapagliflozin
Reporting group description:	
Forxiga®, dapagliflozin 10 mg film-coated tablets. The intervention is a single dose of 50 mg. For further information please refer to: https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf.	
Reporting group title	Placebo
Reporting group description:	
The composition equals the composition of Forxiga® – just with the active ingredient omitted. Active drug and placebo are similar in appearance and smell.	

Primary: Change from 0 to 6 hours in renal cortical oxygenation

End point title	Change from 0 to 6 hours in renal cortical oxygenation
End point description:	
End point type	Primary
End point timeframe:	
Change from 0 to 6 hours	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: second^-1				
least squares mean (standard error)	-1.1 (± 0.7)	1.3 (± 0.7)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 6 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.012 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	-0.6

Notes:

[1] - Calculated with the use of a repeated-measures analysis including terms for treatment, randomisation-sequence, day of visit, blood glucose, time of measurement and interaction between time of measurement and treatment. A low R2* corresponds to a high oxygenation. P-values for comparisons of changes from baseline between dapagliflozin and placebo.

[2] - The least squares mean changes in renal cortical R2* from baseline to six hours were for dapagliflozin -1·1 (SEM 0·7) s-1 and for placebo +1·3 (0·7) s-1 resulting in a difference between interventions of -2·3 s-1 (95% CI -4·0 to -0·6); p=0·012

Primary: Change from 0 to 3 hours in renal cortical oxygenation

End point title	Change from 0 to 3 hours in renal cortical oxygenation

End point description:

The primary outcome was change in renal oxygenation (R2*) measured with quantitative MRI on a 3-T Philips Achieva scanner.

End point type	Primary

End point timeframe:

Time Frame: From baseline to +3 hours from intervention

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: second^-1				
least squares mean (standard error)	0.3 (± 0.6)	0.6 (± 0.6)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 3 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.673
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.9

Primary: 3-hour change in renal medullary oxygenation

End point title	3-hour change in renal medullary oxygenation

End point description:	
End point type	Primary
End point timeframe: change from 0 to 3 hours	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: second^-1				
least squares mean (standard error)	1.4 (± 0.7)	0.7 (± 0.8)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 3 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.588
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	0.7

Primary: 6-hour change in renal medullary perfusion

End point title	6-hour change in renal medullary perfusion
End point description:	
End point type	Primary
End point timeframe: change from 0 to 6 hours	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: second^-1				
least squares mean (standard error)	-0.2 (± 0.8)	1.2 (± 0.6)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 6 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	1

Secondary: 6-hour change in renal cortical perfusion

End point title	6-hour change in renal cortical perfusion
End point description:	
the unit is ml/100g/minute	
End point type	Secondary
End point timeframe:	
Change from 0 to 6 hours in renal cortical perfusion	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: second^-1				
least squares mean (standard error)	5.1 (± 13.3)	8.6 (± 11.2)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 6 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.822
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.7
upper limit	28.8
Variability estimate	Standard error of the mean
Dispersion value	15.1

Secondary: 3-hour change in renal cortical perfusion

End point title	3-hour change in renal cortical perfusion
End point description:	
the unit is ml/100g/minute	
End point type	Secondary
End point timeframe:	
change from 0 to 3 hours	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: second^-1				
least squares mean (standard error)	-11.8 (± 10.3)	-5.7 (± 8.8)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 3 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.53
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-27
upper limit	13.7
Variability estimate	Standard error of the mean
Dispersion value	9.7

Secondary: 6-hour change in renal medullary perfusion

End point title	6-hour change in renal medullary perfusion

End point description:

End point type	Secondary

End point timeframe:

change from 0 to 6 hours

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ml/100g/minute				
least squares mean (standard error)	0.2 (± 3.0)	3.4 (± 3.9)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 6 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.441
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	5.4
Variability estimate	Standard error of the mean
Dispersion value	4

Secondary: 3-hour change in renal medullary oxygenation

End point title	3-hour change in renal medullary oxygenation
End point description:	
End point type	Secondary
End point timeframe:	
change from 0 to 3 hours	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ml/100g/minute				
least squares mean (standard error)	-2.0 (± 2.3)	-0.2 (± 4.8)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 3 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.717
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	8.5
Variability estimate	Standard error of the mean
Dispersion value	4.8

Secondary: 3-hour change in renal artery blood flow

End point title	3-hour change in renal artery blood flow
End point description:	
End point type	Secondary
End point timeframe:	
change from 0 to 3 hours	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ml/minute				
least squares mean (standard error)	-30 (± 15)	-2 (± 8)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 3 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.135
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64
upper limit	10
Variability estimate	Standard error of the mean
Dispersion value	17

Secondary: 6-hour change in renal artery blood flow

End point title	6-hour change in renal artery blood flow
End point description:	
End point type	Secondary
End point timeframe:	
change from 0 to 6 hours	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ml/minute				
least squares mean (standard error)	-3 (± 14)	16 (± 12)		

Statistical analyses

Statistical analysis title	Difference in change from 0 to 6 hours
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.237
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54
upper limit	15
Variability estimate	Standard error of the mean
Dispersion value	16

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events: between February 3, 2020 and October 23, 2020	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Dapagliflozin
Reporting group description: -	

Serious adverse events	Dapagliflozin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dapagliflozin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		

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: I confirm that there were no non-serious adverse events in this mechanistic acute effect study with a single dose of 50 mg dapagliflozin.

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