Clinical trial results:
A Double-blind, Randomized, Phase IV, Mechanistic, Placebo-controlled, Cross-over, Single-center Study to Evaluate the Effects of 5 Weeks Dapagliflozin Treatment on Insulin Sensitivity in Skeletal Muscle in Type 2 Diabetes Mellitus Patients

Summary

EudraCT number	2016-003991-27
Trial protocol	NL
Global end of trial date	04 November 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	D1690C00047

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03338855
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com

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	04 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if dapagliflozin improves skeletal muscle insulin sensitivity expressed as corrected glucose disposal rate (cGDR) in comparison with placebo after 5-week double-blind treatment. Insulin sensitivity was determined using a 2-step euglycemic hyperinsulinemic clamp (EHC) procedure.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation /Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2018
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	Netherlands: 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)	16
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a double-blind, randomized, placebo-controlled, cross-over Phase IV mechanistic study which was conducted in 1 study center in the Netherlands between 05 March 2018 and 04 November 2019.

Pre-assignment

Screening details:

Eligible patients with Type 2 diabetes mellitus were randomized to a specific double-blind treatment sequence (either dapagliflozin then placebo or placebo then dapagliflozin). Each of the 2 treatment periods had a maximum duration of 40 days, separated by a wash-out period of 6 to 8 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10 mg then Placebo

Arm description:

Patients received an oral dose of 10 milligrams (mg) dapagliflozin, once daily for 5 weeks. After a wash-out period of 6 to 8 weeks, matched placebo tablets were taken orally, once daily for 5 weeks.

Arm type	Experimental and Placebo
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Forxiga®, Farxiga®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet was to be taken orally once daily in the morning and at approximately the same time of day during the treatment period.

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:

One tablet was to be taken orally once daily in the morning and at approximately the same time of day during the treatment period.

Arm title	Placebo then Dapagliflozin 10 mg

Arm description:

Patients received placebo tablets (matched to dapagliflozin) taken orally, once daily for 5 weeks. After a wash-out period of 6 to 8 weeks, patients received an oral dose of 10 mg dapagliflozin, once daily for 5 weeks.

Arm type	Experimental and Placebo

Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Forxiga®, Farxiga®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet was to be taken orally once daily in the morning and at approximately the same time of day during the treatment period.

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:

One tablet was to be taken orally once daily in the morning and at approximately the same time of day during the treatment period.

Number of subjects in period 1	Dapagliflozin 10 mg then Placebo	Placebo then Dapagliflozin 10 mg
Started	12	14
Received Treatment in Period 1	12	14
Received Treatment in Period 2	11	14
Completed	11	14
Not completed	1	0
Withdrawn as birth control pill stopped	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin 10 mg then Placebo
Reporting group description:	
Patients received an oral dose of 10 milligrams (mg) dapagliflozin, once daily for 5 weeks. After a wash-out period of 6 to 8 weeks, matched placebo tablets were taken orally, once daily for 5 weeks.	
Reporting group title	Placebo then Dapagliflozin 10 mg
Reporting group description:	
Patients received placebo tablets (matched to dapagliflozin) taken orally, once daily for 5 weeks. After a wash-out period of 6 to 8 weeks, patients received an oral dose of 10 mg dapagliflozin, once daily for 5 weeks.	

Reporting group values	Dapagliflozin 10 mg then Placebo	Placebo then Dapagliflozin 10 mg	Total
Number of subjects	12	14	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	8	16
From 65-84 years	4	6	10
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	63.0	64.4	
standard deviation	± 4.7	± 4.7	-
Sex: Female, Male Units:			
Female	5	1	6
Male	7	13	20
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	12	14	26
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	12	14	26

Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Dapagliflozin 10 mg then Placebo
Reporting group description:	
Patients received an oral dose of 10 milligrams (mg) dapagliflozin, once daily for 5 weeks. After a wash-out period of 6 to 8 weeks, matched placebo tablets were taken orally, once daily for 5 weeks.	
Reporting group title	Placebo then Dapagliflozin 10 mg
Reporting group description:	
Patients received placebo tablets (matched to dapagliflozin) taken orally, once daily for 5 weeks. After a wash-out period of 6 to 8 weeks, patients received an oral dose of 10 mg dapagliflozin, once daily for 5 weeks.	
Subject analysis set title	Dapagliflozin 10 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients received an oral dose of 10 mg dapagliflozin, once daily for 5 weeks in either Treatment Period 1 or Treatment Period 2.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients received an oral dose of placebo, once daily for 5 weeks in either Treatment Period 1 or Treatment Period 2.	

Primary: Corrected Glucose Disposal Rate (cGDR) Measured as Change in Rate of Disposal (Delta RD) Basal vs High Insulin After 5 Weeks of Treatment

End point title	Corrected Glucose Disposal Rate (cGDR) Measured as Change in Rate of Disposal (Delta RD) Basal vs High Insulin After 5 Weeks of Treatment
End point description:	
Skeletal muscle insulin sensitivity was measured as cGDR (referred to as delta RD [basal vs high insulin]) using a 2-step 5.5 hour EHC procedure in combination with infusion of D-glucose (6,6-D2) glucose. Delta RD (basal vs high insulin) was corrected for urinary glucose excretion and measured at the end of Treatment Periods 1 and 2. The evaluable analysis set (clamp) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with important procedure specific protocol deviations regarding the clamp method were excluded.	
End point type	Primary
End point timeframe:	
At end (Week 5) of Treatment Periods 1 and 2	

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: micromole/kilogram body weight/minute				
least squares mean (confidence interval 95%)	8.523 (5.566 to 11.481)	9.592 (6.634 to 12.549)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of delta RD (basal vs high insulin) between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.3047 [2]
Method	Linear Mixed Effects Model
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-1.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.183
upper limit	1.047
Variability estimate	Standard error of the mean
Dispersion value	1.014

Notes:

[1] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.
[2] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Other pre-specified: Change in Endogenous Glucose Production (EGP) After 5 Weeks of Treatment

End point title	Change in Endogenous Glucose Production (EGP) After 5 Weeks of Treatment

End point description:

A 2 step 5.5 hour EHC in combination with infusion of 6,6-D2 glucose was used to determine rates of EGP at the end of Treatment Periods 1 and 2. Results of the change in EGP are presented as delta EGP (basal vs low insulin and basal vs high insulin). The evaluable analysis set (clamp) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with important procedure specific protocol deviations regarding the clamp method were excluded.

End point type	Other pre-specified

End point timeframe:

At end (Week 5) of Treatment Periods 1 and 2

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: micromole/kilogram body weight/minute				
least squares mean (confidence interval 95%)				
Delta EGP (basal vs low insulin)	-4.656 (-5.494 to -3.817)	-2.591 (-3.790 to -2.112)		

Delta EGP (basal vs high insulin)	-10.803 (-11.726 to -9.880)	-8.512 (-9.435 to -7.589)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of delta EGP (basal vs low insulin) between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0036 [4]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-1.705
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.784
upper limit	-0.625
Variability estimate	Standard error of the mean
Dispersion value	0.517

Notes:

[3] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.

[4] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of delta EGP (basal vs high insulin) between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-2.292
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.146
upper limit	-1.438
Variability estimate	Standard error of the mean
Dispersion value	0.409

Notes:

[5] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.

[6] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Other pre-specified: Change in Respiratory Exchange Ratio (RER) from Fasted State to Insulin Stimulated State After 5 Weeks of Treatment

End point title	Change in Respiratory Exchange Ratio (RER) from Fasted State to Insulin Stimulated State After 5 Weeks of Treatment

End point description:

During the indirect calorimetry of the EHC test, respiratory gas exchange was measured using open air circuit respirometry with an automated ventilated hood system. Metabolic flexibility was determined by the change in RER from fasted state to insulin stimulated state at the end of Treatment Periods 1 and 2 and results are presented as delta RER (basal vs high insulin). The evaluable analysis set (indirect calorimetry) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with important procedure specific protocol deviations regarding the indirect calorimetry method were excluded.

End point type	Other pre-specified

End point timeframe:

At end (Week 5) of Treatment Periods 1 and 2

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: micromole/kilogram body weight/minute				
least squares mean (confidence interval 95%)	0.101 (0.080 to 0.122)	0.089 (0.068 to 0.110)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of delta RER (basal vs high insulin) between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1842 [8]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.03

Variability estimate	Standard error of the mean
Dispersion value	0.009

Notes:

[7] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.

[8] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Other pre-specified: 24-Hour RER After 5 Weeks of Treatment

End point title	24-Hour RER After 5 Weeks of Treatment

End point description:

RER was measured before and after meals over a 24-hour period. The evaluable analysis set (chamber) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with important procedure specific protocol deviations regarding the chamber method were excluded.

End point type	Other pre-specified

End point timeframe:

At end (Week 5) of Treatment Periods 1 and 2

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: ratio				
least squares mean (confidence interval 95%)	0.812 (0.803 to 0.821)	0.835 (0.826 to 0.844)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of 24-hour RER between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0001 [10]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	-0.013
Variability estimate	Standard error of the mean
Dispersion value	0.005

Notes:

[9] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.

[10] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Other pre-specified: 24-Hour Energy Expenditure After 5 Weeks of Treatment

End point title	24-Hour Energy Expenditure After 5 Weeks of Treatment

End point description:

Whole body energy expenditure was measured over a 24-hour period. The evaluable analysis set (chamber) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with important procedure specific protocol deviations regarding the chamber method were excluded.

End point type	Other pre-specified

End point timeframe:

At end (Week 5) of Treatment Periods 1 and 2

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: megajoules/day				
least squares mean (confidence interval 95%)	9.519 (9.017 to 10.020)	9.628 (9.126 to 10.130)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of energy expenditure between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.1095 [12]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.245
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.065

Notes:

[11] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.

[12] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Other pre-specified: Body Composition (Fat Mass and Lean Mass) After 5 Weeks of Treatment

End point title	Body Composition (Fat Mass and Lean Mass) After 5 Weeks of Treatment

End point description:

On Day 6, 7 or 8 of the end of treatment visit in both treatment periods, a Dual-energy X-ray absorptiometry (DEXA) scan was used to determine body composition. The evaluable analysis set (DEXA) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with procedure specific protocol deviations regarding the DEXA method were excluded.

End point type	Other pre-specified

End point timeframe:

At end (Week 5) of Treatment Periods 1 and 2

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: grams				
least squares mean (confidence interval 95%)				
Fat Mass	25318.3 (22978.4 to 27658.1)	25564.9 (23225.0 to 27904.8)		
Lean Mass	59929.0 (56762.1 to 63095.8)	60595.4 (57428.5 to 63762.3)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of fat mass between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.6005 [14]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-246.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1209.5
upper limit	716.2
Variability estimate	Standard error of the mean
Dispersion value	464.3

Notes:

[13] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.
[14] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of lean mass between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0376 [16]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-666.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1291
upper limit	-41.9
Variability estimate	Standard error of the mean
Dispersion value	301.1

Notes:

[15] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.
[16] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Other pre-specified: Body Composition (Total Mass) After 5 Weeks of Treatment

End point title	Body Composition (Total Mass) After 5 Weeks of Treatment

End point description:

On Day 6, 7 or 8 of the end of treatment visit in both treatment periods a DEXA scan was used to determine body composition. The evaluable analysis set (DEXA) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with important procedure specific protocol deviations regarding the DEXA method were excluded.

End point type	Other pre-specified

End point timeframe:

At end (Week 5) of Treatment Periods 1 and 2

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: kilograms				
least squares mean (confidence interval 95%)	85.248 (81.608 to 88.888)	86.504 (82.864 to 90.143)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of total mass between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0003 [18]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-1.256
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.854
upper limit	-0.657
Variability estimate	Standard error of the mean
Dispersion value	0.289

Notes:

[17] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.

[18] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Other pre-specified: Fibroblast Growth Factor 21 (FGF21) Area Under the Curve (AUC) in Plasma After 5 Weeks of Treatment

End point title	Fibroblast Growth Factor 21 (FGF21) Area Under the Curve (AUC) in Plasma After 5 Weeks of Treatment

End point description:

From the end of Day 1 until the morning of Day 3 of the end of each treatment visit, the patients stayed in the metabolic chamber (36 hours). During this stay FGF21 was measured in plasma before and after meals and before bed-time to determine the AUC (last 24 hours). The evaluable analysis set (chamber) was a subset of the randomized analysis set, consisting of patients who received at least 1 dose of any investigational product. Any patients with important procedure specific protocol deviations regarding the chamber method were excluded.

End point type	Other pre-specified

End point timeframe:

At end (Week 5) of Treatment Periods 1 and 2

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: nanograms/liter/hour				
least squares mean (confidence interval 95%)	3310.415 (2626.919 to 3993.911)	3554.716 (2871.270 to 4238.212)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Comparison of FGF21 AUC between dapagliflozin and placebo after 5 weeks of treatment was performed using a random effects analysis of variance model.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.1555 [20]
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	-244.301
Confidence interval	
level	95 %
sides	2-sided
lower limit	-590.002
upper limit	101.401
Variability estimate	Standard error of the mean
Dispersion value	165.168

Notes:

[19] - As this is a cross-over study and subject analysis sets are not mutually exclusive, the given automatically calculated number in the statistical analysis reflects the number of data points rather than number of subjects.

[20] - A linear mixed model with treatment group, treatment sequence, and period as fixed effects and patient as random effect.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events (AEs) were reported for an overall time frame up to a maximum of 19 weeks (including both 5-week treatment periods, 6-8 weeks wash-out and 5-10 days safety follow-up after last dose of study drug).

Adverse event reporting additional description:

In this study, collection of AE data was limited to the collection of serious AEs, discontinuation of investigational product due to an AE and potential diabetic ketoacidosis events only. The safety analysis set consisted of all patients who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Dapagliflozin 10mg

Reporting group description:

Patients received an oral dose of 10mg dapagliflozin, once daily for 5 weeks.

Reporting group title	Placebo

Reporting group description:

Patients received placebo tablets (matched to dapagliflozin) taken orally, once daily for 5 weeks.

Serious adverse events	Dapagliflozin 10mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Dapagliflozin 10mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (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: There were no non serious adverse events above the 5% threshold in either reporting group.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2017	Exclusion criterion added to exclude patients who did not want to be informed about unexpected medical findings or did not wish their physician to be informed about coincidental findings. Laboratory safety assessments updated to include serum/plasma potassium. The section entitled "Storage and destruction of Biological Samples" was updated to clarify length of time biological samples were to be retained. Sample size estimation also updated to provide more details of assumptions made and specify software used.
20 June 2018	Exploratory objectives updated to include assessment of effect of dapagliflozin on citrate synthase activity in muscle biopsy. New exploratory objective added to investigate the effect of dapagliflozin on body weight, body mass index (BMI), and systolic and diastolic blood pressure. Inclusion criteria updated to specify that eligible patients could be on a stable dose of dipeptidyl peptidase IV inhibitor treatment for at least 3 months and also to specify patients should have a BMI of ≤ 38 kg/m2. Criteria for withdrawal updated to permit rescreening of patients. The section entitled "Study termination" was added. Biomarker assessments updated to include amino acids in addition to acetylcarnitine. Sample size estimation updated to specify screen failure rate, to ensure enough evaluable patients evenly distributed across the treatment sequences.
13 August 2018	The section entitled "Study termination" was removed.
12 September 2018	Implemented a pre-screening telephone call prior to Visit 1 to explain the study and ask the patients some questions relating to inclusion and exclusion criteria to verify eligibility. Included provision of a lifestyle card to the patient at Visit 2 to inform them of lifestyle advice to be adhered to during the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported