Clinical trial results:
Effect of dapagliflozin, metformin and physical activity on glucose variability, body composition and cardiovascular risk in pre-diabetes (The PRE-D Trial)
- A randomised, parallel, open-label, intervention study

Summary

EudraCT number	2015-001552-30
Trial protocol	DK
Global end of trial date	13 January 2019

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	PRED-D-TRIAL2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02695810
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	Sponsor, Steno Diabetes Center A/S, +45 30791461, krif@steno.dk
Scientific contact	Sponsor, Steno Diabetes Center A/S, +45 30791461, krif@steno.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	18 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective is to compare the short-term effectiveness of three glucose-lowering interventions (physical activity, metformin, and dapagliflozin) on glucose variability, body composition, and cardiometabolic risk factors in overweight or obese individuals with pre-diabetes (HbA1c 6.0-6.4%).

Protection of trial subjects:

None

Background therapy:

All participants received general advice on diet and physical activity based on national Danish recommendations

Evidence for comparator: -

Actual start date of recruitment	01 October 2015
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: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	70
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Inclusion Criteria:
HbA1c: from ≥5.7% (39 mmol/mol) to ≤6.4% (47 mmol/mol)
Age: from ≥30 to ≤70 years of age
BMI ≥25 kg/m2

Exclusion Criteria:
Uncontrolled medical issues including but not limited to cardiovascular pulmonary, rheumatologic, hematologic, oncologic, infectious, gastrointestinal or psychiatric disease; diabetes or

Pre-assignment period milestones

Number of subjects started	120
Number of subjects completed	120

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Participants were randomised at the end of the baseline visit (V1), but were blinded for group allocation untill the end of the baseline period. Staff were blinded to group allocation at V1, but not in the following free-living period. The data analysts were blinded towards group allocation and results were evaluated before unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Metformin

Arm description:

No active treatment in this period

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

Dosage and administration details:

850 mg daily for 1 week and then 850 mg twice daily for the rest of the intervention

Arm title	Dapagliflozin

Arm description:

No active treatment in this period

Arm type	Experimental

Investigational medicinal product name	dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily

Arm title	Exercise

Arm description:

No active treatment in this period

Arm type	Exercise intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Control	Metformin	Dapagliflozin
Started	30	30	30
Completed	30	30	30
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	Exercise
Started	30
Completed	29
Not completed	1
Consent withdrawn by subject	1

Period 2

Period 2 title	Active treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label trial: Neither staff, nor participants were blinded to group allocation during the follow-up period. Data analysts were blinded to groupallocation and results were evaluated by the research group before unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Metformin

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

850 mg daily for 1 week and then 850 mg twice daily for the rest of the intervention

Arm title	Dapagliflozin

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily

Arm title	Exercise

Arm description:

The exercise intervention consisted of unsupervised interval training, 5 days/week, 30 min/session, with alternating 3-min intervals aiming for intensities of ≥75% and ≤60% of peak heart rate by the end of each interval.

Arm type	Exercise intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Control	Metformin	Dapagliflozin
Started	30	30	30
Completed	28	29	28
Not completed	2	1	2
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	1	-	1
Lost to follow-up	-	1	-

Number of subjects in period 2	Exercise
Started	29
Completed	27
Not completed	2
Consent withdrawn by subject	2
Adverse event, non-fatal	-
Lost to follow-up	-

Period 3

Period 3 title	Follow-up (No active treatment)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label trial: Neither staff, nor participants were blinded to group allocation during the follow-up period. Data analysts were blinded to groupallocation and results were evaluated by the research group before unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Metformin

Arm description:

No active treatment in this period

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

Dosage and administration details:

850 mg daily for 1 week and then 850 mg twice daily for the rest of the intervention

Arm title	Dapagliflozin

Arm description:

No active treatment in this period

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

Dosage and administration details:

10 mg once daily

Arm title	Exercise

Arm description:

No active treatment in this period

Arm type	Exercise intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Control	Metformin	Dapagliflozin
Started	28	29	28
Completed	27	29	28
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

Number of subjects in period 3	Exercise
Started	27
Completed	27
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

End points

End points reporting groups

Reporting group title	Control
Reporting group description: -	
Reporting group title	Metformin
Reporting group description:	
No active treatment in this period	
Reporting group title	Dapagliflozin
Reporting group description:	
No active treatment in this period	
Reporting group title	Exercise
Reporting group description:	
No active treatment in this period	
Reporting group title	Control
Reporting group description: -	
Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Dapagliflozin
Reporting group description: -	
Reporting group title	Exercise
Reporting group description:	
The exercise intervention consisted of unsupervised interval training, 5 days/week, 30 min/session, with alternating 3-min intervals aiming for intensities of ≥75% and ≤60% of peak heart rate by the end of each interval.	
Reporting group title	Control
Reporting group description: -	
Reporting group title	Metformin
Reporting group description:	
No active treatment in this period	
Reporting group title	Dapagliflozin
Reporting group description:	
No active treatment in this period	
Reporting group title	Exercise
Reporting group description:	
No active treatment in this period	

Primary: Glycemic variability

End point title	Glycemic variability
End point description:	
Mean amplitude of glycemic excursions calculated based on a 7-days continous glucose monitoring period.	
End point type	Primary
End point timeframe:	
Analysed as comparisons between relative changes from baseline (period 1) to end-of-treatment (period 2) for the intervention groups compared with the control group.	

End point values	Control	Control	Control	Metformin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	28	26[1]	30
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	1.5 (1.2 to 1.8)	1.7 (1.4 to 2.3)	1.9 (1.5 to 2.7)	1.6 (1.1 to 1.8)

Notes:

[1] - One participant missing at random

End point values	Metformin	Metformin	Dapagliflozin	Dapagliflozin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	29	30	26
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	1.6 (1.3 to 2.0)	1.5 (1.4 to 1.9)	1.7 (1.5 to 2.4)	1.6 (1.2 to 2.2)

End point values	Dapagliflozin	Exercise	Exercise	Exercise
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27[2]	30	27	27
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	1.9 (1.3 to 2.5)	1.8 (1.4 to 2.8)	1.7 (1.2 to 2.5)	1.8 (1.3 to 2.0)

Notes:

[2] - One participant missing at random

Statistical analyses

Statistical analysis title	Primary end-point analysis - Met/Con

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Metformin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.991
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.1
upper limit	19.4
Variability estimate	Standard error of the mean

Notes:

[3] - Metformin was hypothesized to be non-superior to controls for improving MAGE

Statistical analysis title	Primary end-point analysis - Dap/Con

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Dapagliflozin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.042
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-17.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.8
upper limit	-0.7
Variability estimate	Standard error of the mean

Notes:

[4] - Dapagliflozin was hypothesized to be superior to controls for improving MAGE; minimally important difference of 0.5mmol/L (approx. 30%)

Statistical analysis title	Primary end-point analysis - Exe/Con

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Exercise
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.067
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	1.2
Variability estimate	Standard error of the mean

Notes:

[5] - Exercise was hypothesized to be superior to controls for improving MAGE; minimally important difference of 0.5mmol/L (approx. 30%)

Statistical analysis title	Follow-up - Dap/Met

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Metformin v Dapagliflozin

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.256
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.6
upper limit	7.8
Variability estimate	Standard error of the mean

Notes:

[6] - Descriptive

Statistical analysis title	Primary end-point analysis - Exe/Met

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Metformin v Exercise
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.065
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-15.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	1.1
Variability estimate	Standard error of the mean

Notes:

[7] - Exercise was hypothesized to be superior to metformin for improving MAGE; minimally important difference of 0.5mmol/L (approx. 30%)

Statistical analysis title	Follow-up - Exe/Dap

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Dapagliflozin v Exercise

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.651
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.2
upper limit	15.1
Variability estimate	Standard error of the mean

Notes:

[8] - Descriptive

Statistical analysis title	Follow-up - Met/Con

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Metformin
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.291
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.9
upper limit	8.5
Variability estimate	Standard error of the mean

Notes:

[9] - Descriptive

Statistical analysis title	Follow-up - Dap/Con

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Dapagliflozin

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.032
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.7
upper limit	-1.7
Variability estimate	Standard error of the mean

Notes:

[10] - Descriptive

Statistical analysis title	Follow-up - Exe/Con

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Exercise v Control
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.009
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.5
upper limit	-5.7
Variability estimate	Standard error of the mean

Notes:

[11] - Descriptive

Statistical analysis title	Primary end-point analysis - Dap/Met

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Metformin v Dapagliflozin

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.041
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.9
upper limit	-0.8
Variability estimate	Standard error of the mean

Notes:

[12] - Dapagliflozin was hypothesized to be superior to metformin for improving MAGE; minimally important difference of 0.5mmol/L (approx. 30%).

Statistical analysis title	Follow-up - Exe/Met

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Metformin v Exercise
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.11
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.7
upper limit	3.4
Variability estimate	Standard error of the mean

Notes:

[13] - Descriptive

Statistical analysis title	Mid treatment analysis - Dap/Con

Statistical analysis description:

Analysis performed after 6 weeks of intervention. Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Dapagliflozin

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.047
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-16.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.3
upper limit	-0.2
Variability estimate	Standard error of the mean

Notes:

[14] - Descriptive

Statistical analysis title	Primary end-point - Exe/Dap

Statistical analysis description:

Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Exercise v Dapagliflozin
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.815
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.8
upper limit	22.5
Variability estimate	Standard error of the mean

Notes:

[15] - Exercise was hypothesized to be superior to metformin for improving MAGE; minimally important difference of 0.5mmol/L (approx. 30%)

Statistical analysis title	Mid treatment analysis - Met/Con

Statistical analysis description:

Analysis performed after 6 weeks of intervention. Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Metformin

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.379
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.4
upper limit	10.2
Variability estimate	Standard error of the mean

Notes:

[16] - Descriptive

Statistical analysis title	Mid treatment analysis - Exe/Con

Statistical analysis description:

Analysis performed after 6 weeks of intervention. Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Control v Exercise
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.059
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.3
upper limit	0.6
Variability estimate	Standard error of the mean

Notes:

[17] - Descriptive

Statistical analysis title	Mid treatment analysis - Dap/Met

Statistical analysis description:

Analysis performed after 6 weeks of intervention. Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Metformin v Dapagliflozin

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.257
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.5
upper limit	7.8
Variability estimate	Standard error of the mean

Notes:

[18] - Descriptive

Statistical analysis title	Mid treatment analysis - Exe/Dap

Statistical analysis description:

Analysis performed after 6 weeks of intervention. Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Dapagliflozin v Exercise
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.903
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.5
upper limit	20.9
Variability estimate	Standard error of the mean

Notes:

[19] - Descriptive

Statistical analysis title	Mid treatment analysis - Exe/Met

Statistical analysis description:

Analysis performed after 6 weeks of intervention. Intention-to-treat analysis. Data were log-transformed for analysis and results were back-transformed and represented as the difference in relative changes: i.e. if group A changed 20% between visit 1 and 2 (A2/A1 = 1.2) and group B changed 10% (B2/B1 = 1.1), then the relative change between group A and B is 1.2/1.1 = 9.1%

Comparison groups	Exercise v Metformin

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.305
Method	Mixed models analysis
Parameter estimate	Difference between relative changes
Point estimate	-8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.4
upper limit	8.7
Variability estimate	Standard error of the mean

Notes:

[20] - Descriptive

Adverse events

Adverse events information	
Timeframe for reporting adverse events: During participation in the trial, systematically recorded at visits.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Metformin
Reporting group description: No active treatment in this period	
Reporting group title	Control
Reporting group description: -	
Reporting group title	Exercise
Reporting group description: No active treatment in this period	
Reporting group title	Dapagliflozin
Reporting group description: No active treatment in this period	

Serious adverse events	Metformin	Control	Exercise
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 29 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events		0	
Respiratory, thoracic and mediastinal disorders			
lung cancer	Additional description: Further details unknown.		
alternative dictionary used: None X			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dapagliflozin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Respiratory, thoracic and mediastinal disorders			
lung cancer	Additional description: Further details unknown.		
alternative dictionary used: None X			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.8 %

Non-serious adverse events	Metformin	Control	Exercise
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 30 (80.00%)	4 / 30 (13.33%)	7 / 29 (24.14%)
Investigations			
Vasovagal reaction	Additional description: In relation to exercise test		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Hypertension			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Rash	Additional description: Rash in relation to the use of CGM plaster.		
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	1 / 29 (3.45%)
occurrences (all)	0	2	1
Dehydration	Additional description: Mild		
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0

Night sweats			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 30 (23.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	7	0	0
Abdominal discomfort			
subjects affected / exposed	4 / 30 (13.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0
Constipation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Increased appetite			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	9 / 30 (30.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	9	0	0
Nausea			
subjects affected / exposed	4 / 30 (13.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0
Minor bleeding per rectum			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Reduced appetite			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Vomiting			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash	Additional description: Bilateral rash on hands		
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Increased sweating			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Itchiness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Balanoposthitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Pyuria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Candida infection	Additional description: Vaginal		
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Urine odour abnormal			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Lower extremity		
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	5 / 29 (17.24%)
occurrences (all)	0	0	5
Pain in lower back			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Infected insect bite			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 29 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Dapagliflozin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 30 (56.67%)		
Investigations			
Vasovagal reaction	Additional description: In relation to exercise test		
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Hypertension			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Rash	Additional description: Rash in relation to the use of CGM plaster.		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Dehydration	Additional description: Mild		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Abdominal discomfort			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Flatulence			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Increased appetite			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Minor bleeding per rectum			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Reduced appetite			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash	Additional description: Bilateral rash on hands		
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Increased sweating			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Itchiness			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Mood swings			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Balanoposthitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pyuria			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Candida infection	Additional description: Vaginal		
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Polyuria			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Urine odour abnormal			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Lower extremity		
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pain in lower back			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Erysipelas			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Infected insect bite			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2016	Because of a slow recruitment rate, the inclusion criterion for HbA1c was expanded from 42-47 mmol/mol (criterion suggested by the International Expert Committee) to 39-47 mmol/mol (criterion suggested by the American Diabetes Association).
11 July 2016	The number of participants to be included was reduced from 160 to 120.

Notes:

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/28592573