

**Clinical trial results:****A Double-Blind, Randomized, Parallel Group, Phase IV Study To Investigate The Effects Of Dapagliflozin On Cardiac Substrate Uptake, Myocardial Efficiency And Myocardial Contractile Work In Type 2 Diabetes Patients****Summary**

EudraCT number	2017-003820-58
Trial protocol	FI SE
Global end of trial date	19 March 2019

Results information

Result version number	v1 (current)
This version publication date	27 March 2020
First version publication date	27 March 2020

Trial information**Trial identification**

Sponsor protocol code	D1690C00063
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03387683
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, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical, +1 877-240-9479, 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	19 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of dapagliflozin on cardiac substrate uptake, myocardial efficiency, and myocardial contractile work versus placebo after 6 weeks of double-blind treatment in patients with type 2 diabetes.

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	28 February 2018
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	Sweden: 15
Country: Number of subjects enrolled	Finland: 38
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	23
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifty three patients with type 2 diabetes and on a stable dose of metformin for at least 6 weeks were enrolled in 1 study center in Sweden and 1 center in Finland. The first patient was enrolled on 28 February 2018 and the last patient's last visit was on 19 March 2019.

Pre-assignment

Screening details:

Eligible patients were aged between 40 and 75 years, had type 2 diabetes for at least 6 months and had no significant coronary artery disease symptoms. Patients were randomized in a 1:1 ratio, to receive 10 milligrams (mg) dapagliflozin or placebo.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10 mg

Arm description:

Patients were randomized to receive an oral dose of 10 mg dapagliflozin, once daily, for 6 weeks.

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

Dosage and administration details:

One tablet of 10 mg dapagliflozin to be taken orally, once daily, in the morning.

Arm title	Placebo
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Arm description:

Patients were randomized to receive an oral dose of placebo (to match 10 mg dapagliflozin), once daily, for 6 weeks.

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:

One matched placebo tablet be taken orally, once daily, in the morning.

Number of subjects in period 1	Dapagliflozin 10 mg	Placebo
Started	27	26
Completed	25	26
Not completed	2	0
In receipt of disallowed medication	1	-
Did not receive treatment	1	-

Baseline characteristics

Reporting groups

Reporting group title	Dapagliflozin 10 mg
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Reporting group description:

Patients were randomized to receive an oral dose of 10 mg dapagliflozin, once daily, for 6 weeks.

Reporting group title	Placebo
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Reporting group description:

Patients were randomized to receive an oral dose of placebo (to match 10 mg dapagliflozin), once daily, for 6 weeks.

Reporting group values	Dapagliflozin 10 mg	Placebo	Total
Number of subjects	27	26	53
Age, Customized Units: Subjects			
<65 years	12	11	23
≥65 years	15	15	30
Sex: Female, Male Units: Subjects			
Female	8	15	23
Male	19	11	30
Race/Ethnicity, Customized Units: Subjects			
White	27	26	53

End points

End points reporting groups

Reporting group title	Dapagliflozin 10 mg
Reporting group description:	Patients were randomized to receive an oral dose of 10 mg dapagliflozin, once daily, for 6 weeks.
Reporting group title	Placebo
Reporting group description:	Patients were randomized to receive an oral dose of placebo (to match 10 mg dapagliflozin), once daily, for 6 weeks.

Primary: Adjusted Mean Change from Baseline in Global Longitudinal Strain of the Left Ventricle (GLSLV) at End of Treatment.

End point title	Adjusted Mean Change from Baseline in Global Longitudinal Strain of the Left Ventricle (GLSLV) at End of Treatment.
End point description:	Patients underwent magnetic resonance imaging (MRI) examination to determine the GLSLV, which is expressed as a percentage. The least square mean (LSM) change from baseline estimates were generated from an analysis of covariance (ANCOVA) model with treatment and baseline value of the endpoint as covariates.
End point type	Primary
End point timeframe:	Baseline (Day 1) and end of treatment (Day 42)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Percent				
least squares mean (confidence interval 95%)	0.30769 (-0.35001 to 0.96538)	-0.00352 (-0.66121 to 0.65417)		

Statistical analyses

Statistical analysis title	Difference in LSM (Placebo - Dapagliflozin 10 mg)
Statistical analysis description:	The LSM estimate and corresponding p-value were obtained from a linear model with treatment and baseline value of the endpoint as covariates.
Comparison groups	Dapagliflozin 10 mg v Placebo

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.504 ^[1]
Method	ANCOVA
Parameter estimate	Difference in LSM
Point estimate	0.31121
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.619
upper limit	1.24141
Variability estimate	Standard error of the mean
Dispersion value	0.46184

Notes:

[1] - Statistical significance was inferred at a (2-sided) 0.05 level.

Secondary: Adjusted Mean Change from Baseline in Myocardial Efficiency at End of Treatment.

End point title	Adjusted Mean Change from Baseline in Myocardial Efficiency at End of Treatment.
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End point description:

A clinical radiologic assessment of acquired computed tomography and positron emission tomography (CT-PET)-[11C]-acetate images was performed to determine myocardial efficiency. The myocardial efficiency calculation was based on an estimate of energy used for producing LV contractile work (mean arterial pressure (MAP) x stroke volume (SV) x heart rate (HR) / myocardial mass) compared to the total cardiac work (calculated based on the total myocardial oxygen consumption per myocardial mass) and is expressed as a percentage. The LSM change from baseline estimates, were generated from an ANCOVA model with treatment and baseline value of the endpoint as covariates.

Results are presented for patients in the CT-PET-[11C]-acetate evaluable analysis set who, as per clinical judgment, had fasted and abstained from products containing nicotine, caffeine and alcohol for at least 6 hours prior to both of the times when CT-PET-[11C]-acetate measurements were taken.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and end of treatment (Day 42)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Percent				
least squares mean (confidence interval 95%)	-0.71474 (-3.74654 to 2.31706)	-2.46443 (-5.49623 to 0.56737)		

Statistical analyses

Statistical analysis title	Difference in LSM (Placebo - Dapagliflozin 10 mg)
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Statistical analysis description:

The LSM estimate and corresponding p-value were obtained from a linear model with treatment and

baseline value of the endpoint as covariates.

Comparison groups	Placebo v Dapagliflozin 10 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.427 [2]
Method	ANCOVA
Parameter estimate	Difference in LSM
Point estimate	1.74969
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.64837
upper limit	6.14775
Variability estimate	Standard error of the mean
Dispersion value	2.18363

Notes:

[2] - Statistical significance was inferred at a (2-sided) 0.05 level.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from start of treatment until 1 week after end of treatment (Day 1 to Day 49).

Adverse event reporting additional description:

Collection of AE data was limited to the collection of Serious AEs and AEs leading to the discontinuation of study medication only. Data is presented for the Safety Analysis Set which consisted of all subjects who received at least one dose of study medication during the treatment period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Dapagliflozin 10 mg
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Reporting group description:

Patients were randomized to receive an oral dose of 10 mg dapagliflozin, once daily, for 6 weeks.

Reporting group title	Placebo
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Reporting group description:

Patients were randomized to receive an oral dose of placebo (to match 10 mg dapagliflozin), once daily, for 6 weeks.

Serious adverse events	Dapagliflozin 10 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (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: 0 %

Non-serious adverse events	Dapagliflozin 10 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (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: In this Study the collection of AE data was limited to collection of serious adverse events and adverse events leading to discontinuation of study medication only as per the protocol.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2018	<ul style="list-style-type: none">• Included additional scanner type (integrated MRI/PET machine) for assessment of PET-related endpoints to provide the possibility to use several machines to optimize PET assessment availability.• Updated regarding PET assessment with [¹⁸F]- fluoro-6-thia-heptadecanoic acid (FTHA) tracer. The [¹⁸F]-FTHA examinations were exploratory and were not to be performed in all the randomized patients. Instead, a minimum of 40 and a maximum of 44 randomized patients were to undergo the examinations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported