Clinical trial results:
A study of the effects of dapagliflozin on ambulatory aortic pressure, arterial stiffness and urine albumin excretion in patients with type 2 diabetes.

Summary

EudraCT number	2015-005288-17
Trial protocol	GR
Global end of trial date	10 June 2019

Results information

Result version number	v1 (current)
This version publication date	09 April 2022
First version publication date	09 April 2022

Trial information

Trial identification

Sponsor protocol code	ESR-15-10964

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hellenic Society for Medical Education
Sponsor organisation address	Tsimiski 44, Thessaloniki, Greece,
Public contact	Asterios Karagiannis, President of the Hellenic Society for Medical Education, Hellenic Society for Medical Education, 0030 2310992845, astkar@med.auth.gr
Scientific contact	Asterios Karagiannis, President of the Hellenic Society for Medical Education, Hellenic Society for Medical Education, 0030 2310992845, astkar@med.auth.gr

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 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2019
Global end of trial reached?	Yes
Global end of trial date	10 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the present study was to investigate the effect of dapagliflozin on ambulatory aortic pressure in patients with type 2 DM.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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)	57
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted across 3 sites in Thessaloniki. The first subject was recruited in Sep 2016; with the last subject last visit planned for Sep 2019, on Feb 2019 Astra-Zeneca notified the sponsor/investigators of its intention to terminate the financial support, leading to premature trial termination with last randomized patient in Mar 2019.

Pre-assignment

Screening details:

A total of 123 participants consented to participate in the study, of which 38 were screen failures; 85 participants were finally randomized (43 to dapagliflozin and 42 to placebo).

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, Data analyst, Carer, Assessor

Blinding implementation details:

The Sponsor, the CRO, investigators, study staff, and the patients were blinded to study drug assignment during the double-blind period of the trial, from the time of randomization until the database lock. The following methods were used to ensure the blinding: a)Randomization data were kept confidential until the time of unblinding and were not accessible by anyone else involved in the study, b) the identity of the treatments was concealed by the use of study drugs that were all identical.

Arms

Are arms mutually exclusive?	Yes
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:

Dapagliflozin for oral administration was supplied as a 10 mg film-coated tablet (green, plain, diamond shaped) containing dapagliflozin propanediol monohydrate equivalent to 10 mg of dapagliflozin. The dosage was dapagliflozin 10 mg (p.o.) q24h for 12 weeks.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Placebo for oral administration was supplied as a film-coated tablet of identical color and texture (i.e. green, plain, diamond shaped). The dosage was Placebo (p.o.) q24h for 12 weeks

Number of subjects in period 1	Dapagliflozin	Placebo
Started	43	42
Completed	41	39
Not completed	2	3
Consent withdrawn by subject	1	3
Refuse to perform 24-h ABPM at study-end	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Dapagliflozin	Placebo	Total
Number of subjects	43	42	85
Age categorical Units: Subjects			
Adults (18-64 years)	29	28	57
From 65-84 years	14	14	28
Age continuous Units: years			
arithmetic mean	61.74	60.64	
standard deviation	± 6.73	± 9.35	-
Gender categorical Units: Subjects			
Female	20	21	41
Male	23	21	44

End points

End points reporting groups

Reporting group title	Dapagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: The difference between the groups of dapagliflozin and placebo in the change of 24-hour systolic aortic pressure recorded with the Mobil-O-Graph device at study-end.

End point title	The difference between the groups of dapagliflozin and placebo in the change of 24-hour systolic aortic pressure recorded with the Mobil-O-Graph device at study-end.
End point description:	

End point type	Primary
End point timeframe:	
Basline and study-end (12 weeks).	

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: mmHg				
arithmetic mean (standard deviation)	-4.12 (± 8.00)	-0.65 (± 7.77)		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.046
Method	t-test, 2-sided

Notes:

[1] - Analysis of study outcomes included all randomized participants (intention-to-treat principle). We used the last observation carried forward method to handle missing data

Secondary: The difference between the groups of dapagliflozin and placebo in the change of 24-hour diastolic aortic pressure recorded with the Mobil-O-Graph device at study-end.

End point title	The difference between the groups of dapagliflozin and placebo in the change of 24-hour diastolic aortic pressure recorded with the Mobil-O-Graph device at study-end.

End point description:

End point type	Secondary

End point timeframe:

Baseline and study-end (12 weeks).

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: mmHg				
arithmetic mean (standard deviation)	-1.63 (± 5.23)	0.16 (± 5.99)		

Statistical analyses

Statistical analysis title	Secondary endpoint
Comparison groups	Placebo v Dapagliflozin
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.144
Method	t-test, 2-sided

Notes:

[2] - Analysis of study outcomes included all randomized participants (intention-to-treat principle). We used the last observation carried forward method to handle missing data

Secondary: The difference between the groups of dapagliflozin and placebo in the change of 24-hour brachial systolic blood pressure recorded with the Mobil-O-Graph device at study-end.

End point title	The difference between the groups of dapagliflozin and placebo in the change of 24-hour brachial systolic blood pressure recorded with the Mobil-O-Graph device at study-end.

End point description:

End point type	Secondary

End point timeframe:

Baseline and study-end (12 weeks).

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: mmHg				
arithmetic mean (standard deviation)	-5.80 (± 9.48)	-0.10 (± 8.70)		

Statistical analyses

Statistical analysis title	Secondary endpoint
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.005
Method	t-test, 2-sided

Notes:

[3] - Analysis of study outcomes included all randomized participants (intention-to-treat principle). We used the last observation carried forward method to handle missing data

Secondary: The difference between the groups of dapagliflozin and placebo in the change of 24-hour brachial diastolic blood pressure recorded with the Mobil-O-Graph device at study-end.

End point title	The difference between the groups of dapagliflozin and placebo in the change of 24-hour brachial diastolic blood pressure recorded with the Mobil-O-Graph device at study-end.

End point description:

End point type	Secondary

End point timeframe:

Baseline and study-end (12 weeks).

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: mmHg				
arithmetic mean (standard deviation)	-2.23 (± 5.26)	0.10 (± 5.70)		

Statistical analyses

Statistical analysis title	Secondary endpoint
Comparison groups	Dapagliflozin v Placebo

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.054
Method	t-test, 2-sided

Notes:

[4] - Analysis of study outcomes included all randomized participants (intention-to-treat principle). We used the last observation carried forward method to handle missing data

Secondary: The difference between the groups of dapagliflozin and placebo in the change of 24-hour pulse wave velocity recorded with the Mobil-O-Graph device at study-end.

End point title	The difference between the groups of dapagliflozin and placebo in the change of 24-hour pulse wave velocity recorded with the Mobil-O-Graph device at study-end.

End point description:

End point type	Secondary

End point timeframe:

Baseline and study-end (12 weeks).

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: m/sec				
arithmetic mean (standard deviation)	-0.16 (± 0.32)	0.02 (± 0.27)		

Statistical analyses

Statistical analysis title	Secondary endpoint
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.007
Method	t-test, 2-sided

Notes:

[5] - Analysis of study outcomes included all randomized participants (intention-to-treat principle). We used the last observation carried forward method to handle missing data

Secondary: The difference between the groups of dapagliflozin and placebo in the change of albumin/creatinine ratio at study-end.

End point title	The difference between the groups of dapagliflozin and placebo in the change of albumin/creatinine ratio at study-end.

End point description:

End point type	Secondary

End point timeframe:

Baseline and study-end (12 weeks).

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: mg/g				
median (inter-quartile range (Q1-Q3))	0.02 (-3.63 to 3.71)	-0.73 (-2.74 to 2.18)		

Statistical analyses

Statistical analysis title	Secondary endpoint
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.447
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Analysis of study outcomes included all randomized participants (intention-to-treat principle). We used the last observation carried forward method to handle missing data

Secondary: The difference between the groups of dapagliflozin and placebo in the change of glycosylated hemoglobin at study-end

End point title	The difference between the groups of dapagliflozin and placebo in the change of glycosylated hemoglobin at study-end

End point description:

End point type	Secondary

End point timeframe:

Baseline and study-end (12 weeks).

End point values	Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: percent				
arithmetic mean (standard deviation)	-0.57 (± 0.74)	-0.09 (± 0.66)		

Statistical analyses

Statistical analysis title	Secondary endpoint
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.002
Method	t-test, 2-sided

Notes:

[7] - Analysis of study outcomes included all randomized participants (intention-to-treat principle). We used the last observation carried forward method to handle missing data

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events (AEs) were followed as appropriate during the study (from baseline to study-end).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	Dapagliflozin group
Reporting group description: -	
Reporting group title	Placebo group
Reporting group description: -	

Serious adverse events	Dapagliflozin group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Basal cell carcinoma			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dapagliflozin group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 43 (23.26%)	10 / 42 (23.81%)	
Cardiac disorders			
Hypotension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	

Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	2 / 42 (4.76%) 2	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	0 / 42 (0.00%) 0	
Immune system disorders Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	1 / 42 (2.38%) 1	
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	1 / 42 (2.38%) 1	
Respiratory, thoracic and mediastinal disorders Upper respiratory tract infection subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1 0 / 43 (0.00%) 0	1 / 42 (2.38%) 1 1 / 42 (2.38%) 1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 42 (2.38%) 1	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Prostatic specific antigen increased subjects affected / exposed occurrences (all) Lithiasis subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3 1 / 43 (2.33%) 1 0 / 43 (0.00%) 0	0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 1 / 42 (2.38%) 1	
Musculoskeletal and connective tissue			

disorders Osteoarthritis subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 42 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2016	Following the changes in the labeling of the investigational product (dapagliflozin), the appropriate changes in inclusion criteria [(a) from "Age >18 and <70 years old" to "Age >18 and <75 years old" and (b) from "Patients on stable dose of metformin of at least 1500 mg for the past 3 months" to "Patients on monotherapy or combination of two of the following type of antidiabetic agents: metformin, sulphonylurea, DDP-4 inhibitor, or insulin for the past 3 months")] and exclusion criteria (from "Patients on antidiabetic drugs other than metformin" to "Patients on GLP-1 receptor agonist or pioglitazone") were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported