Clinical trial results:
An 8-week, single centre, randomized, parallel-group, double-blind, placebo controlled phase IV trial to evaluate Dapagliflozin 10 mg once daily effects on insulin resistance in subjects with type 2 diabetes mellitus

Summary

EudraCT number	2014-005377-36
Trial protocol	FI
Global end of trial date	29 November 2016

Results information

Result version number	v1 (current)
This version publication date	12 May 2017
First version publication date	12 May 2017

Trial information

Trial identification

Sponsor protocol code	D1690C00025

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca R&D
Sponsor organisation address	SE-431 83, Molndal, Sweden,
Public contact	Anna Maria Langkilde, CVMD Development, 46 317761000, annamaria.langkilde@astrazeneca.com
Scientific contact	Anna Maria Langkilde, CVMD Development, 46 317761000, annamaria.langkilde@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	29 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2016
Global end of trial reached?	Yes
Global end of trial date	29 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if dapagliflozin 10 mg once daily when compared to placebo improves insulin sensitivity in skeletal muscle after 8 weeks of treatment in type 2 diabetes mellitus (T2D) patients

Protection of trial subjects:

At any time, subjects were free to discontinue IP or withdraw from the study (i.e., IP and assessments), without prejudice to further treatment. A subject that decided to discontinue IP was always asked about the reason(s) and the presence of any AEs. If possible, they were seen and assessed by an Investigator. If a subject withdrew after at least 4 weeks of treatment, the assessment normally scheduled at Visit 4 could be performed at the time of the withdrawal (except when the informed consent had been withdrawn). AEs were followed up and all remaining IP was returned by the subject.

Background therapy:

Stable metformin, dipeptidyl peptidase-4 inhibitors (DPP-IV) or sulphonylurea treatment, or on stable treatment with metformin in combination with sulphonylurea or DPP-IV

Evidence for comparator:

Placebo comparator represents absence of additional treatment with an anti-diabetic agent.

Actual start date of recruitment	23 March 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	Finland: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	13
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects were recruited at a single invenstigative site in Turku, Finland

Pre-assignment

Screening details:

A total of 55 subjects were screened and 32 were randomised and treated.

Period 1

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

Blinding implementation details:

Double-blind

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10 MG

Arm description:

Dapagliflozin 10 MG once daily

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	A10BX09
Other name	Forxiga, Farxiga
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg taken orally once daily

Arm title	Placebo

Arm description:

Placebo once daily

Arm type	Placebo
Investigational medicinal product name	Placebo matching Dapagliflozin 10 MG
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet QD

Number of subjects in period 1	Dapagliflozin 10 MG	Placebo
Started	16	16
Completed	15	16
Not completed	1	0
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin 10 MG
Reporting group description: Dapagliflozin 10 MG once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	

Reporting group values	Dapagliflozin 10 MG	Placebo	Total
Number of subjects	16	16	32
Age Categorical Units: Subjects			
Adults (18-64 years)	8	11	19
From 65-84 years	8	5	13
Age Continuous Units: years			
arithmetic mean	59.9	62.1	
standard deviation	± 7.4	± 8.4	-
Gender Categorical Units: Subjects			
Female	3	4	7
Male	13	12	25
Race Units: Subjects			
White	16	16	32

End points

End points reporting groups

Reporting group title	Dapagliflozin 10 MG
Reporting group description: Dapagliflozin 10 MG once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	

Primary: Adjusted mean change from baseline in skeletal muscle insulin-stimulated glucose uptake

End point title	Adjusted mean change from baseline in skeletal muscle insulin-stimulated glucose uptake
End point description: Least square mean estimates obtained from analysis of covariance model of change from baseline with model terms for treatment, sex, and baseline	
End point type	Primary
End point timeframe: From baseline to Week 8	

End point values	Dapagliflozin 10 MG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: umol/min/kg				
least squares mean (standard deviation)	0.8404 (± 3.3226)	-0.3304 (± 5.1869)		

Statistical analyses

Statistical analysis title	Skeletal muscle insulin-stimulated glucose uptake
Statistical analysis description: Comparison of least square mean mean change from baseline in skeletal muscle insulin-stimulated glucose uptake from analysis of covariance model of change from baseline in skeletal muscle insulin-stimulated glucose uptake with terms for baseline, sex, and treatment	
Comparison groups	Dapagliflozin 10 MG v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9984
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.003

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.0742
upper limit	3.0681

Secondary: Adjusted mean change from baseline in adipose tissue insulin-stimulated glucose uptake

End point title	Adjusted mean change from baseline in adipose tissue insulin-stimulated glucose uptake

End point description:

Least square mean estimates obtained from analysis of covariance model of change from baseline with model terms for treatment, sex, and baseline

End point type	Secondary

End point timeframe:

From baseline to Week 8

End point values	Dapagliflozin 10 MG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: umol/min/kg				
least squares mean (standard error)	1.0412 (± 1.4992)	-0.6403 (± 1.3644)		

Statistical analyses

Statistical analysis title	Adipose tissue insulin-stimulated glucose uptake

Statistical analysis description:

Comparison of least square mean mean change from baseline in adipose tissue insulin-stimulated glucose uptake from analysis of covariance model of change from baseline in adipose tissue insulin-stimulated glucose uptake with terms for baseline, sex, and treatment

Comparison groups	Dapagliflozin 10 MG v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.3794
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.6815
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1788
upper limit	5.5418

Notes:

[1] - Least square mean estimates obtained from analysis of covariance model of change from baseline with model terms for treatment, sex, and baseline

Secondary: Adjusted mean change from baseline in liver insulin-stimulated glucose uptake

End point title	Adjusted mean change from baseline in liver insulin-stimulated glucose uptake

End point description:

Least square mean estimates obtained from analysis of covariance model of change from baseline with model terms for treatment and baseline

End point type	Secondary

End point timeframe:

From baseline to Week 8

End point values	Dapagliflozin 10 MG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: umol/min/kg				
least squares mean (standard error)	0.2681 (± 1.7477)	1.5896 (± 1.52)		

Statistical analyses

Statistical analysis title	Liver insulin-stimulated gluocose uptake

Statistical analysis description:

Comparison of least square mean mean change from baseline in liver insulin-stimulated glucose uptake from analysis of covariance model of change from baseline in liver insulin-stimulated glucose uptake with terms for baseline, sex, and treatment

Comparison groups	Dapagliflozin 10 MG v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5317
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.3215
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6017
upper limit	2.9587

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first day of double-blind study medication to either four (non-serious AEs) or thirty (SAEs) days beyond the last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Dapalgliflozin 10 MG
Reporting group description: Dapagliflozin 10 MG once daily added to stable metformin, sulphonylurea or DPP-IV alone or metformin in combination with sulphonylurea or DPP-IV	
Reporting group title	Placebo
Reporting group description: Placebo once daily added to stable metformin, sulphonylurea or DPP-IV alone or metformin in combination with sulphonylurea or DPP-IV	

Serious adverse events	Dapalgliflozin 10 MG	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (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: 5 %

Non-serious adverse events	Dapalgliflozin 10 MG	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)	7 / 16 (43.75%)	
Investigations			
Blood gluocse decrease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
orthostatic hypotension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hypoaesthesia	Additional description: NOS		
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Thirst			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	4 / 16 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Infections and infestations			

Balanitis	Additional description: NOS		
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infections NEC			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Sinusitis	Additional description: NOS		
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported