



Clinical trial results:

A Multicentre, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III Study to Evaluate the Glycaemic Efficacy and Renal Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment (CKD 3A) Who Have Inadequate Glycaemic Control

Summary

EudraCT number	2015-000804-24
Trial protocol	SE IT ES CZ PL
Global end of trial date	07 November 2017

Results information

Result version number	v1 (current)
This version publication date	01 November 2018
First version publication date	01 November 2018

Trial information

Trial identification

Sponsor protocol code	D1690C00024
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02413398
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Global Clinical Leader-Dapagliflozin AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
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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	07 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2017
Global end of trial reached?	Yes
Global end of trial date	07 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the glycaemic efficacy and renal safety of dapagliflozin (FORXIGA™/FARXIGA™) in patients with T2DM and moderate renal impairment (chronic kidney disease stage 3A [CKD 3A]; estimated glomerular filtration rate [eGFR] 45 to 59 mL/min/1.73 m²) who have inadequate glycaemic control (glycated haemoglobin [HbA1c] ≥7% and ≤11%) under usual care

Protection of trial subjects:

Two safety adjudication committees were established for this study. An independent Hepatic Adjudication Committee, blinded to the treatment of the patients, determined the probability that drug-induced liver injury (DILI) was the cause of liver-related abnormalities, including, but not limited to: • Hepatic events temporally related to death (within 30 days of death) • Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3× upper limit of normal (ULN) and total bilirubin (TB) >2× ULN (within 14 days of the AST and/or ALT elevation • AST and/or ALT >10× ULN All potential events of diabetic ketoacidosis (DKA) were recorded in the electronic case report form (eCRF) and submitted to an independent DKA Adjudication Committee. The DKA Committee Type 2 Diabetes Mellitus (T2DM) assessed available information on each potential DKA event and classified the event in accordance with the definitions in the DKA Adjudication Charter T2DM. The DKA Adjudication Committee was kept blinded to the IP treatment received by each patient with a potential DKA event in the clinical study.

Background therapy:

For those patients on a background therapy that included insulin, each patient's baseline insulin therapy should have remained unchanged wherever possible throughout the double blind treatment period. At randomisation, the assignment to either dapagliflozin 10 mg or placebo (1:1) was stratified on background antidiabetic medication.

Evidence for comparator: -

Actual start date of recruitment	15 June 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	Bulgaria: 53
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	United States: 91

Worldwide total number of subjects	321
EEA total number of subjects	181

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)	110
From 65 to 84 years	211
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 88 study centres (medical facilities) in 8 countries. This included 9 centres in Bulgaria, 17 centres in Canada, 7 centres in Czech Republic, 8 centres in Italy, 7 centres in Poland, 9 centres in Spain, 4 centres in Sweden and 27 centres in the United States (US).

Pre-assignment

Screening details:

At enrolment, obtaining written informed consent prior to any study procedure or change in medical therapy was required by the protocol. Consenting patients were assessed to ensure that they met eligibility criteria. Patients who did not meet these criteria were not enrolled in the study.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10mg QD

Arm description:

10 mg Tablets, Oral, Once daily, 24 weeks

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin 10mg QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10mg QD

Arm title	Placebo QD
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Arm description:

Matching Placebo, 10 mg Tablets, Oral, Once daily, 24 weeks

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

Dosage and administration details:

Placebo QD

Number of subjects in period 1	Dapagliflozin 10mg QD	Placebo QD
Started	160	161
Completed	156	154
Not completed	4	7
Consent withdrawn by subject	1	1
Other Eligibility criteria	1	2
Lost to follow-up	2	4

Baseline characteristics

Reporting groups

Reporting group title	Dapagliflozin 10mg QD
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Reporting group description:

10 mg Tablets, Oral, Once daily, 24 weeks

Reporting group title	Placebo QD
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Reporting group description:

Matching Placebo, 10 mg Tablets, Oral, Once daily, 24 weeks

Reporting group values	Dapagliflozin 10mg QD	Placebo QD	Total
Number of subjects	160	161	321
Age, Customized Units: Subjects			
< 65 Years	64	46	110
>= 65 Years	96	115	211
Age Continuous Units: years			
arithmetic mean	65.3	66.2	
standard deviation	± 6.22	± 6.49	-
Sex: Female, Male Units: Subjects			
Female	69	70	139
Male	91	91	182
Race/Ethnicity, Customized Units: Subjects			
American Indian Or Alaska Native	2	0	2
Asian	5	8	13
Black Or African American	11	12	23
Other	1	1	2
White	141	140	281
Body Mass Index Units: kg/m ²			
arithmetic mean	32.6	31.6	
standard deviation	± 4.7	± 5.0	-
Estimated Glomerular Filtration Rate (eGFR) Units: mL/min/1.73 m ²			
arithmetic mean	51.8	51.6	
standard deviation	± 4.1	± 3.8	-
Urine Albumin-to-Creatinine Ratio (UACR) Units: mg/g			
arithmetic mean	226.91	246.52	
standard deviation	± 566.67	± 775.49	-

End points

End points reporting groups

Reporting group title	Dapagliflozin 10mg QD
Reporting group description:	
10 mg Tablets, Oral, Once daily, 24 weeks	
Reporting group title	Placebo QD
Reporting group description:	
Matching Placebo, 10 mg Tablets, Oral, Once daily, 24 weeks	

Primary: Adjusted mean change from baseline in HbA1c at Week 24

End point title	Adjusted mean change from baseline in HbA1c at Week 24
End point description:	
To compare the mean change from baseline in HbA1c between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes, CKD stage 3A, and moderate renal impairment (CKD 3A; eGFR 45-59 mL/min/1.73m ²).	
End point type	Primary
End point timeframe:	
At Week 24	

End point values	Dapagliflozin 10mg QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	159		
Units: percent				
arithmetic mean (standard error)	-0.37 (± 0.10)	-0.03 (± 0.10)		

Statistical analyses

Statistical analysis title	MMRM
Statistical analysis description:	
Difference in adjusted mean change from baseline (MMRM model)	
Comparison groups	Dapagliflozin 10mg QD v Placebo QD
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Adjusted mean percent change from baseline in total body weight at Week 24.

End point title	Adjusted mean percent change from baseline in total body weight at Week 24.
End point description: To compare the mean percent change from baseline in total body weight between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes, CKD stage 3A, and moderate renal impairment (CKD 3A; eGFR 45-59 mL/min/1.73m ²).	
End point type	Secondary
End point timeframe: At Week 24	

End point values	Dapagliflozin 10mg QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	161		
Units: percent				
arithmetic mean (standard error)				
Adjusted mean percent change from baseline	-3.42 (± 0.32)	-2.02 (± 0.32)		

Statistical analyses

Statistical analysis title	Body weight (% , change from baseline)
Statistical analysis description: Difference in adjusted mean percent change from baseline (MMRM)	
Comparison groups	Dapagliflozin 10mg QD v Placebo QD
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	-0.69
Variability estimate	Standard error of the mean
Dispersion value	0.37

Secondary: Adjusted mean change from baseline in FPG at Week 24.

End point title	Adjusted mean change from baseline in FPG at Week 24.
End point description:	
To compare the mean change from baseline in FPG between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes, CKD stage 3A, and moderate renal impairment (CKD 3A; eGFR 45-59 mL/min/1.73m ²)..	
End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Dapagliflozin 10mg QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	134		
Units: mg/dL				
arithmetic mean (standard error)				
Change in FPG at Week 24	-21.4637 (± 5.2053)	-4.8722 (± 5.1267)		

Statistical analyses

Statistical analysis title	Change in FPG at 24 weeks
Statistical analysis description:	
Difference in adjusted mean change from baseline versus placebo (MMRM)	
Comparison groups	Dapagliflozin 10mg QD v Placebo QD
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-16.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.73
upper limit	-6.46

Variability estimate	Standard error of the mean
Dispersion value	5.15

Secondary: Adjusted mean change from baseline in seated SBP at Week 24.

End point title	Adjusted mean change from baseline in seated SBP at Week 24.
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End point description:

To compare the mean change from baseline in seated systolic blood pressure (SBP) between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes, CKD stage 3A, and moderate renal impairment (CKD 3A; eGFR 45-59 mL/min/1.73m²).

End point type	Secondary
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End point timeframe:

At Week 24

End point values	Dapagliflozin 10mg QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	145		
Units: mmHg				
arithmetic mean (standard error)				
Seated SBP (mmHg) change from baseline to Week 24	-4.8 (± 1.5)	-1.7 (± 1.5)		

Statistical analyses

Statistical analysis title	SBP change from baseline to Week 24
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Statistical analysis description:

Difference in adjusted mean change from baseline vs. placebo (MMRM)

Comparison groups	Dapagliflozin 10mg QD v Placebo QD
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	1.6

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

AEs were collected from the first dose of double-blind treatment through the end of treatment. SAEs were recorded from the time of Informed Consent through the end of the follow-up period.

Adverse event reporting additional description:

No non-serious AEs met the >5% reporting threshold by Preferred Term.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Dapagliflozin 10mg QD
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Reporting group description:

10 mg Tablets, Oral, Once daily, 24 weeks

Reporting group title	Placebo
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Reporting group description:

Matching Placebo, 10 mg Tablets, Oral, Once daily, 24 weeks

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: No non-serious AEs had an incidence of $\geq 5\%$.

Serious adverse events	Dapagliflozin 10mg QD	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 160 (5.63%)	14 / 161 (8.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 160 (0.63%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gingival bleeding			
subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 160 (0.63%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint swelling			

subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diabetic gangrene			
subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	0 / 160 (0.00%)	1 / 161 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 160 (0.63%)	0 / 161 (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: 5 %

Non-serious adverse events	Dapagliflozin 10mg QD	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 160 (0.00%)	0 / 161 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2016	The number of sites was updated. Updated the benefit/risk and ethical assessment section of CSP to include the potential risk of DKA. The upper limit of BMI range was increased to 45 kg/m ² . Exclusion criterion #37 and text related to restrictions on metformin in CSP Section 7.7 were modified by including "or" to allow a difference between Investigator's judgment and local guidelines. Exclusion criterion #38 was updated to explicitly state that ongoing treatment with GLP-1 agonist was an exclusion criterion. The sample specimen has been corrected to state "blood glucose" instead of "fasting plasma glucose."
01 April 2016	Inclusion/Exclusion criteria were updated: 1. HbA1c was removed from Visit 3 and the eGFR criterion modified. 2. Exclusion criterion #24 was introduced 3. Exclusion criterion #47 (48, in the current version) was modified. Blood volume was updated (reduced by 2 mL to 61 mL).
17 January 2017	Exclusion criteria #39 was included to provide clarity that rapid or short acting insulin were never allowed in the study from the version 1.0 of the CSP. New CSP Section 5.2.5.6 was added to include information about the reporting and adjudication of DKA events in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported