Clinical trial results:
A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate
the Safety and Efficacy of Dapagliflozin 10mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a background
combination of Metformin and Sulfonylurea

Summary

EudraCT number	2011-002231-26
Trial protocol	DE CZ SK ES
Global end of trial date	12 August 2013

Results information

Result version number	v1 (current)
This version publication date	12 May 2016
First version publication date	12 May 2016

Trial information

Trial identification

Sponsor protocol code	D1693C00005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01392677
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden1, Molndal, Sweden, SF-431 83
Public contact	Eva Johnsson, Astra Zeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Eva Johnsson, Astra Zeneca, ClinicalTrialTransparency@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	18 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the change from baseline in HbA1c to week 24 between dapagliflozin 10 mg in combination with metformin and SU and placebo in combination with metformin and SU.

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 Conference on Harmonisation/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The investigator at each center ensured that the patient, parent, guardian, or legal representative (as appropriate) was given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. The patient, parent, guardian, or legal representative (as appropriate) were notified that they were free to discontinue from the study at any time and were given the opportunity to ask questions and allowed time to consider the information provided.

Background therapy:

Stable dose combination therapy of metformin at least 1500 mg each day and maximum tolerated dose which must be at least half maximum dose of sulfonylurea for at least 8 weeks prior to enrolment.

Evidence for comparator:

Placebo-controlled.

Actual start date of recruitment	24 October 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 55
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Slovakia: 36
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Czech Republic: 28
Worldwide total number of subjects	218
EEA total number of subjects	163

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)	142
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of 859 participants enrolled, 736 completed the qualification phase. Of these 597 subjects were randomized and 596 received treatment and 262 were excluded due to adverse events (4), incorrect enrollment (229), withdrawn consent (23), lost to follow-up (2), and other reasons (4).

Pre-assignment

Screening details:

During enrollment, diet and life-style advice was given to participants and was reinforced during a placebo lead-in period. Dose of anti-hyperglycemic combination therapy of metformin >= 1500 mg/day and maximum tolerated dose which must be at least half the maximum dose of sulfonylurea for at least 8 weeks prior to enrollment were to remain stable.

Period 1

Period 1 title	24-week Double-Blind (Full Analysis Set) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

Double-blind

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo plus metformin plus sulfonylurea

Arm description:

Placebo

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:

QD

Arm title	Dapagliflozin 10 mg plus metformin plus sulfonylurea

Arm description:

Dapagliflozn 10 mg

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

Dosage and administration details:

10 mg oral administration

Number of subjects in period 1[1]	Placebo plus metformin plus sulfonylurea	Dapagliflozin 10 mg plus metformin plus sulfonylurea
Started	108	108
Completed	101	101
Not completed	7	7
Consent withdrawn by subject	-	2
Adverse event, non-fatal	3	1
Other reason not completed	4	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline summaries represent the full analysis set (FAS) and was provided to correspond with the analysis set evaluated in efficacy analyses. This population required subjects to receive at least one dose of study medication, and to have baseline and post-treatment assessments available for at least one efficacy parameter.The number of subjects in the FAS is less than the the number worldwide subjects enrolled in the trial

Baseline characteristics

Reporting groups	
Reporting group title	Placebo plus metformin plus sulfonylurea
Reporting group description: Placebo	
Reporting group title	Dapagliflozin 10 mg plus metformin plus sulfonylurea
Reporting group description: Dapagliflozn 10 mg	

Reporting group values	Placebo plus metformin plus sulfonylurea	Dapagliflozin 10 mg plus metformin plus sulfonylurea	Total
Number of subjects	108	108	216
Age categorical Units: Subjects			
Adults (18-64 years)	72	69	141
From 65-74 years	26	30	56
75 years and over	10	9	19
Age Continuous | Units: Years			
arithmetic mean	60.9	61.1	
standard deviation	± 9.24	± 9.65	-
Gender, Male/Female Units: Participants			
Female	48	62	110
Male	60	46	106
Body Mass Index Category			
Percent			
Units: Subjects			
< 25 kg/m^2	2	6	8
>= 25 kg/m^2 - <27 kg/m^2	11	12	23
>=27 kg/m^2 - <30 kg/m^2	26	23	49
>=30 kg/m^2	69	67	136
Race			
Race			
Units: Subjects			
White	102	104	206
Black/African-American	1	0	1
Asian	4	3	7
Other	1	1	2
Ethnicity Units: Subjects			
Hispanic/Latino	1	1	2
Not Hispanic/Latino	107	107	214

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Randomized subjects that received at least 1 dose of double-blind study medication, with a baseline and at least 1 post-baseline assessment for an efficacy paramter.

Reporting group values	Full Analysis Set		
Number of subjects	216		
Age categorical Units: Subjects			
Adults (18-64 years)	141		
From 65-74 years	56		
75 years and over	19		
Age Continuous | Units: Years			
arithmetic mean	61		
standard deviation	± 9.42		
Gender, Male/Female Units: Participants			
Female	110		
Male	106		
Body Mass Index Category			
Percent			
Units: Subjects			
< 25 kg/m^2	8		
>= 25 kg/m^2 - <27 kg/m^2	23		
>=27 kg/m^2 - <30 kg/m^2	49		
>=30 kg/m^2	136		
Race			
Race			
Units: Subjects			
White	206		
Black/African-American	1		
Asian	7		
Other	2		
Ethnicity Units: Subjects			
Hispanic/Latino	2		
Not Hispanic/Latino	214		

End points

End points reporting groups

Reporting group title	Placebo plus metformin plus sulfonylurea
Reporting group description: Placebo	
Reporting group title	Dapagliflozin 10 mg plus metformin plus sulfonylurea
Reporting group description: Dapagliflozn 10 mg	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Randomized subjects that received at least 1 dose of double-blind study medication, with a baseline and at least 1 post-baseline assessment for an efficacy paramter.	

Primary: Adjusted mean change from baseline in Hemoglobin A1C (HbA1c) at Week 24 (Repeated Measures Model [RMM])

End point title	Adjusted mean change from baseline in Hemoglobin A1C (HbA1c) at Week 24 (Repeated Measures Model [RMM])
End point description: HbA1c was measured as percent of hemoglobin by a central laboratory. Data after rescue medication was excluded from this analysis. Baseline was defined as the last assessment prior to the startdate and time of the first dose of the double-blind study medication. In cases where time of the first dose or time of the assessment was not available, baseline was defined as the last assessment onor prior to the date of the first dose of the double-blind study medication. HbA1c measurements were obtained during the qualification and lead-in periods and on Day 1 and Weeks 4, 8, 12, 16, and 24 in the double-blind period.	
End point type	Primary
End point timeframe: From Baseline to Week 24	

End point values	Placebo plus metformin plus sulfonylurea	Dapagliflozin 10 mg plus metformin plus sulfonylurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	108		
Units: Percent				
least squares mean (standard error)	-0.17 (± 0.073)	-0.86 (± 0.0714)		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis
Statistical analysis description: H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0	
Comparison groups	Placebo plus metformin plus sulfonylurea v Dapagliflozin 10 mg plus metformin plus sulfonylurea

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	-0.49
Variability estimate	Standard error of the mean
Dispersion value	0.1022

Notes:

[1] - Significant at alpha=0.05 (2-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives

Secondary: Adjusted mean change from baseline in FPG at Week 24 (Last Observation Carried Forward [LOCF])

End point title	Adjusted mean change from baseline in FPG at Week 24 (Last Observation Carried Forward [LOCF])

End point description:

Secondary endpoints were tested using sequential testing procedure and are presented in hierarchical order. Data after rescue medication was excluded from this analysis. Fasting plasma glucose was measured as milligrams per deciliter (mg/dL) by a central laboratory. Baseline was defined as the last assessment prior to the start date and time of the first dose of the double-blind study medication. In cases where time of the first dose or time of the assessment was not available, baseline was defined as the last assessment on or prior to the date of the first dose of the double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo plus metformin plus sulfonylurea	Dapagliflozin 10 mg plus metformin plus sulfonylurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	108		
Units: mg/dL				
least squares mean (standard error)	-0.78 (± 3.4424)	-34.23 (± 3.4262)		

Statistical analyses

Statistical analysis title	First Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Placebo plus metformin plus sulfonylurea v Dapagliflozin 10 mg plus metformin plus sulfonylurea

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-33.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.08
upper limit	-23.82
Variability estimate	Standard error of the mean
Dispersion value	4.8846

Notes:

[2] - Last Observation Carried Forward (LOCF)

[3] - Significant at alpha=0.05 (2-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives

Secondary: Adjusted Mean Change From Baseline in Total Body Weight at Week 24 (Last Observation Carried Forward [LOCF])

End point title	Adjusted Mean Change From Baseline in Total Body Weight at Week 24 (Last Observation Carried Forward [LOCF])

End point description:

Secondary endpoints were tested using sequential testing procedure and are presented in hierarchical order. Adjusted mean change from baseline in total body weight at Week 24 (or the last postbaseline measurement prior to Week 24 if no Week 24 assessment was available was determined. Data after rescue medication was excluded from this analysis. Baseline was defined as the last assessment prior to the start date and time of the first dose of the double-blind study medication. In cases where time of the first dose or time of the assessment was not available, baseline was defined as the last assessment on or prior to the date of the first dose of the double-blind study medication. Body weight measurements were obtained during the qualification and lead-in periods and on Day 1and Weeks 4, 8, 16, and 24 of the double-blind period.

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo plus metformin plus sulfonylurea	Dapagliflozin 10 mg plus metformin plus sulfonylurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	108		
Units: kg				
least squares mean (standard error)	-0.58 (± 0.258)	-2.65 (± 0.258)		

Statistical analyses

Statistical analysis title	Second Secondary Endpoint Analysis

Statistical analysis description:	
HA: mean(treat) minus mean(placebo) =/= 0	
Comparison groups	Placebo plus metformin plus sulfonylurea v Dapagliflozin 10 mg plus metformin plus sulfonylurea
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	-1.35
Variability estimate	Standard error of the mean
Dispersion value	0.3651

Notes:

[4] - Last Observation Carried Forward (LOCF)

[5] - Significant at alpha=0.05 (2-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives

Secondary: Percentage of Participants Achieving a Therapeutic Glycemic Response (Hemoglobin A1c [HbA1C]) <7.0% at Week 24 (Last Observation Carried Forward [LOCF])

End point title	Percentage of Participants Achieving a Therapeutic Glycemic Response (Hemoglobin A1c [HbA1C]) <7.0% at Week 24 (Last Observation Carried Forward [LOCF])

End point description:

Secondary endpoints were tested using sequential testing procedure and are presented in hierarchical order. Percent adjusted for baseline HbA1c. Therapeutic glycemic response is defined as HbA1c <7.0%. Data after rescue medication was excluded from this analysis. HbA1c was measured as a percent of hemoglobin.

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo plus metformin plus sulfonylurea	Dapagliflozin 10 mg plus metformin plus sulfonylurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	108		
Units: Percentage of participants				
least squares mean (standard error)	11.1 (± 2.884)	31.8 (± 4.319)		

Statistical analyses

Statistical analysis title	Third Secondary Endpoint Analysis
Statistical analysis description:	
H0: proportion(treat) minus proportion (placebo) = 0 versus the alternative HA: proportion (treat) minus proportion (placebo) =/= 0	
Comparison groups	Placebo plus metformin plus sulfonylurea v Dapagliflozin 10 mg plus metformin plus sulfonylurea
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001 [7]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.7
upper limit	30.6
Variability estimate	Standard error of the mean
Dispersion value	5.056

Notes:

[6] - Last Observation Carried Forward (LOCF)

[7] - Significant at alpha=0.05 (2-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives

Secondary: Adjusted Mean Change from Baseline in Seated Systolic Blood Pressure at Week 8 (Last Observation Carried Forward [LOCF])

End point title	Adjusted Mean Change from Baseline in Seated Systolic Blood Pressure at Week 8 (Last Observation Carried Forward [LOCF])

End point description:

Secondary endpoints were tested using sequential testing procedure and are presented in hierarchical order. Adjusted mean change from baseline in total body weight at Week 24 (or the last postbaseline measurement prior to Week 24 if no Week 24 assessment was available was determined.) Data after rescue medication was excluded from this analysis. Baseline was defined as the last assessment prior to the start date and time of the first dose of the double-blind study medication. In cases where time of the first dose or time of the assessment was not available, baseline was definedas the last assessment on or prior to the date of the first dose of the double-blind study medication. Systolic blood pressure measurements were obtained during the qualification and lead-in Periods and on Day 1 and Weeks 4, 8, 16, and 24 of the double-blind period.

End point type	Secondary

End point timeframe:

From Baseline to week 8

End point values	Placebo plus metformin plus sulfonylurea	Dapagliflozin 10 mg plus metformin plus sulfonylurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: mmHg				
least squares mean (standard error)	-0.27 (± 1.1782)	-4.04 (± 1.1782)		

Statistical analyses

Statistical analysis title	Fourth Secondary Endpoint Analysis
Statistical analysis description:	
H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0	
Comparison groups	Placebo plus metformin plus sulfonylurea v Dapagliflozin 10 mg plus metformin plus sulfonylurea
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.025 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.05
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	1.6677

Notes:

[8] - Last Obaservation Carried Forward (LOCF)

[9] - Significant at alpha=0.05 (2-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Non-serious / serious adverse events on or after the first day and on or prior to the last day of the 52-week double-blind treatment plus 4/30 days or up to follow-up visit if earlier, or up to and including the start date of extension period if earlier.

Adverse event reporting additional description:

Participants were questioned at each study visit about the occurrence of any health problems and any examination conducted at a study visit was assessed in comparison to the status at study entry.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Dapagliflozin 10mg plus metformin plus sulfonylurea

Reporting group description:

Dapagliflozin 10mg once daily plus background combination of metformin and sulfonylurea

Reporting group title	Placebo plus metformin plus sulfonylurea

Reporting group description:

Placebo once daily plus background combination of metformin and sulfonylurea

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: The number of non-serious AEs was not reported in the clinical study report in accordance with safety analysis conventions which required the numbers and percentages of subjects that experienced at least one non-serious adverse event. As the number of non-serious AEs and the corresponding numbers and percentages of subjects that experienced at least one non-serious event were not both available in the clinical study report, the absence of complete data as required could not be reported

Serious adverse events	Dapagliflozin 10mg plus metformin plus sulfonylurea	Placebo plus metformin plus sulfonylurea	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 109 (6.42%)	8 / 109 (7.34%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
renal cell carcinoma			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm	Additional description: Benign Lung Neoplasm		

subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
peripheral arterial occlusive disease			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular injuries NEC	Additional description: Vascular Rupture		
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Penis deviation	Additional description: Phimosis		
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
aortic valve stenosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
arrhythmia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Bleeding intracranial	Additional description: Intracranial Haemorrhage		
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemia cerebral	Additional description: Transient Ischaemic Attack		

subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatic neuralgia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (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			
Pelvic organ injury	Additional description: Pelvic Prolapse		
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyp of corpus uteri			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural disorder	Additional description: Haemothorax		
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
calculus ureteric			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
sympathetic posterior cervical syndrome			

subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: Muskuloskeletal		
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (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	0 / 109 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal pneumonia	Additional description: Pneumonia NOS		
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (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 plus metformin plus sulfonylurea	Placebo plus metformin plus sulfonylurea	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Last observation carried forward (LOCF) was used for analyses of secondary endpoints. All endpoints excluded data after rescue.Disposition for the full analysis set had fewer subjects than adverse event summaries, and fewer subjects than enrolled.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25592197