Clinical trial results:
A Multi-Center, Randomised, Double-Blind, Active-Controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Saxagliptin 5 mg Co-administered with Dapagliflozin 5 mg compared to Saxagliptin 5 mg or Dapagliflozin 5 mg all given as Add-on therapy to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Alone

Summary

EudraCT number	2015-005406-11
Trial protocol	DE CZ
Global end of trial date	15 July 2017

Results information

Result version number	v1 (current)
This version publication date	22 July 2018
First version publication date	22 July 2018

Trial information

Trial identification

Sponsor protocol code	D1683C00005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02681094
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Södertälje, Södertälje, Sweden, S-151 85
Public contact	Information Centre, AstraZeneca AB, Information Centre, AstraZeneca AB, +1 800 2369933, information.centre@astrazeneca.com
Scientific contact	Global Clinical Leader, AstraZeneca, +46 766 346712, 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	15 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2017
Global end of trial reached?	Yes
Global end of trial date	15 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of the change from baseline glycated haemoglobin (HbA1c) achieved with the co-dministered saxagliptin 5 mg and dapagliflozin 5 mg to either agent individually after 24 weeks

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 on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. At each site, subject was given full and adequate oral and written information about the nature, purpose, possible benefit and risk of the study. Subject was given opportunity to ask questions and time to consider the information provided. Subjects signed informed consent form (ICF) before conducting any procedure specifically for the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 2016
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	Canada: 100
Country: Number of subjects enrolled	United States: 299
Country: Number of subjects enrolled	Czech Republic: 101
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Mexico: 109
Country: Number of subjects enrolled	Russian Federation: 196
Worldwide total number of subjects	870
EEA total number of subjects	166

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)	652
From 65 to 84 years	217
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 119 sites in 6 countries: Canada, Czech Republic, Germany, Mexico, Russia, and United States (US). Approximately 900 subjects were to be randomized. Subjects with Type 2 Diabetes (T2DM) inadequately controlled on metformin alone were randomized in this study.

Pre-assignment

Screening details:

Subjects had screening (Visit 0) at 1 week prior to enrolment to screen the eligibility based on non-fasting sample of Glycated haemoglobin (Hb A1c); results of HbA1c determined enrolment based on inclusion/exclusion criteria. An abbreviated informed consent form was signed and review of concomitant or other medications/therapies were performed.

Period 1

Period 1 title	1 - Modified full analysis set
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Randomized subjects received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin + Saxagliptin + Metformin

Arm description:

Randomized participants received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin + Saxagliptin + Metformin
Investigational medicinal product code	
Other name	Dapagliflozin: Farxiga™ Saxagliptin: ONGLYZA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 5 mg and saxagliptin 5 mg tablets as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Arm title	Dapagliflozin + Metformin

Arm description:

Randomized participants received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)

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

Dosage and administration details:

Dapagliflozin 5 mg and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Arm title	Saxagliptin + Metformin

Arm description:

Randomized participants received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Saxagliptin + Metformin
Investigational medicinal product code	
Other name	Saxagliptin: ONGLYZA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Saxagliptin 5 mg and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Number of subjects in period 1	Dapagliflozin + Saxagliptin + Metformin	Dapagliflozin + Metformin	Saxagliptin + Metformin
Started	290	289	291
Completed	290	289	291

Period 2

Period 2 title	2 -Modified Enrolled subjects set
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Dapagliflozin + Saxagliptin + Metformin

Arm description:

Randomized participants received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin + Saxagliptin + Metformin
Investigational medicinal product code	
Other name	Dapagliflozin: Farxiga™ Saxagliptin: ONGLYZA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 5 mg and saxagliptin 5 mg tablets as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Arm title	Dapagliflozin + Metformin

Arm description:

Randomized participants received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin + Metformin
Investigational medicinal product code	
Other name	Dapagliflozin: Farxiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 5 mg and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Arm title	Saxagliptin + Metformin

Arm description:

Randomized participants received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Saxagliptin + Metformin
Investigational medicinal product code	
Other name	Saxagliptin: ONGLYZA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Saxagliptin 5 mg and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Number of subjects in period 2	Dapagliflozin + Saxagliptin + Metformin	Dapagliflozin + Metformin	Saxagliptin + Metformin
Started	293	294	296
Completed treatment	273	276	283
Completed	256	255	243
Not completed	37	39	53
Severe non-compliance to protocol	2	-	1
Lack of therapeutic response	1	5	14
Subject decision	7	10	9
Adverse event, non-fatal	10	4	1
Not specified	6	6	7
Study-specific discontinuation criteria	11	13	20
No treatment given	-	1	1

Period 3

Period 3 title	3 - Enrolled subjects set
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin + Saxagliptin + Metformin

Arm description:

Randomized participants received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin + Saxagliptin + Metformin
Investigational medicinal product code	
Other name	Dapagliflozin: Farxiga™ Saxagliptin: ONGLYZA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 5 mg and saxagliptin 5 mg tablets as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Arm title	Dapagliflozin + Metformin

Arm description:

Randomized participants received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin + Metformin
Investigational medicinal product code	
Other name	Dapagliflozin: Farxiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 5 mg and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Arm title	Saxagliptin + Metformin

Arm description:

Randomized participants received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)

Arm type	Experimental
Investigational medicinal product name	Saxagliptin + Metformin
Investigational medicinal product code	
Other name	Saxagliptin: ONGLYZA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Saxagliptin 5 mg and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally) tablet QD orally

Number of subjects in period 3	Dapagliflozin + Saxagliptin + Metformin	Dapagliflozin + Metformin	Saxagliptin + Metformin
Started	301	302	302
Completed treatment	281	284	289
Completed	261	261	248
Not completed	40	41	54
Severe non-compliance to protocol	2	-	1
Study specific discontinuation criteria	14	15	21
Lack of therapeutic response	1	5	14
Subject decision	7	10	9
Adverse event, non-fatal	10	4	1
Not specified	6	6	7
No treatment given	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin + Saxagliptin + Metformin
Reporting group description:	
Randomized participants received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)	
Reporting group title	Dapagliflozin + Metformin
Reporting group description:	
Randomized participants received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)	
Reporting group title	Saxagliptin + Metformin
Reporting group description:	
Randomized participants received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)	

Reporting group values	Dapagliflozin + Saxagliptin + Metformin	Dapagliflozin + Metformin	Saxagliptin + Metformin
Number of subjects	290	289	291
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	212	219	221
From 65-84 years	78	69	70
85 years and over	0	1	0
Age Continuous Units: Years			
arithmetic mean	57.2	55.9	57.0
standard deviation	± 10.68	± 10.94	± 9.94
Sex: Female, Male Units: Subjects			
Female	148	137	134
Male	142	152	157
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	3	0
Asian	9	9	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	17	24
White	265	257	258
More than one race	0	0	0
Unknown or Not Reported	5	3	3
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	99	95	99
Not Hispanic or Latino	191	194	192
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	870		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	652		
From 65-84 years	217		
85 years and over	1		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	419		
Male	451		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4		
Asian	24		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	51		
White	780		
More than one race	0		
Unknown or Not Reported	11		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	293		
Not Hispanic or Latino	577		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Dapagliflozin + Saxagliptin + Metformin

Reporting group description:

Randomized participants received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Dapagliflozin + Metformin

Reporting group description:

Randomized participants received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Saxagliptin + Metformin

Reporting group description:

Randomized participants received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Dapagliflozin + Saxagliptin + Metformin

Reporting group description:

Randomized participants received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Dapagliflozin + Metformin

Reporting group description:

Randomized participants received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Saxagliptin + Metformin

Reporting group description:

Randomized participants received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Dapagliflozin + Saxagliptin + Metformin

Reporting group description:

Randomized participants received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Dapagliflozin + Metformin

Reporting group description:

Randomized participants received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Saxagliptin + Metformin

Reporting group description:

Randomized participants received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)

Primary: Change from baseline in HbA1c at Week 24

End point title	Change from baseline in HbA1c at Week 24

End point description:

To demonstrate the superiority of the change from baseline HbA1c achieved with the co-administered saxagliptin 5 mg and dapagliflozin 5 mg to either agent individually after 24 weeks. Results were presented for the modified full analysis set. Note: Baseline was defined as the last assessment on or prior to the date of the first dose of the study medication.

End point type	Primary

End point timeframe:

At week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Dapagliflozin + Metformin	Saxagliptin + Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	284	280	288	
Units: Percentage (%)				
least squares mean (standard error)	-1.03 (± 0.0558)	-0.63 (± 0.0560)	-0.69 (± 0.0551)	

Statistical analyses

Statistical analysis title	Dapa + Saxa + Met Versus Dapa + Met
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Dapagliflozin + Metformin
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	-0.24

Statistical analysis title	Dapa + Saxa + Met Versus Saxa + Met
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Saxagliptin + Metformin
Number of subjects included in analysis	572
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.19

Secondary: Proportion of subjects achieving HbA1c <7.0% at 24 weeks

End point title	Proportion of subjects achieving HbA1c <7.0% at 24 weeks

End point description:

To demonstrate the effect of the co-administered saxagliptin 5 mg and dapagliflozin 5 mg to either agent individually on proportion of patients achieving therapeutic glycaemic response after 24 weeks. Therapeutic glycaemic response was defined as an HbA1c value at Week 24 <7.0% irrespective of whether subject received rescue medication. Subjects who did not had an HbA1c measurement at Week 24 were regarded as non-responders. Results were presented for the modified full analysis set.

End point type	Secondary

End point timeframe:

After week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Dapagliflozin + Metformin	Saxagliptin + Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	290	289	291	
Units: Percentages of response rate				
number (not applicable)				
Responder|	124	63	83	
Response rate|	42.8	21.8	28.5	
Adjusted response rate|	41.6	21.8	29.8	

Statistical analyses

Statistical analysis title	Dapa + Saxa + Met Versus Dapa + Met
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Dapagliflozin + Metformin
Number of subjects included in analysis	579
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Method of Zhang, Tsiatis, and Davidian
Parameter estimate	Risk difference (RD)
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	26.9

Statistical analysis title	Dapa + Saxa + Met Versus Saxa + Met

Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Saxagliptin + Metformin
Number of subjects included in analysis	581
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0018
Method	Method of Zhang, Tsiatis, and Davidian
Parameter estimate	Risk difference (RD)
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.4
upper limit	19.1

Secondary: Change in fasting plasma glucose at 24 weeks

End point title	Change in fasting plasma glucose at 24 weeks

End point description:

To demonstrate the effect of the co-administered saxagliptin 5 mg and dapagliflozin 5mg to either agent individually on fasting plasma glucose after 24 weeks. Results were presented for the modified full analysis set. Note: Baseline was defined as the last assessment on or prior to the date of the first dose of the study medication.

End point type	Secondary

End point timeframe:

After week 24

End point values	Dapagliflozin + Saxagliptin + Metformin	Dapagliflozin + Metformin	Saxagliptin + Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	284	278	287	
Units: Milligrams per deciliter (mg/dL)				
least squares mean (standard error)	-27.53 (± 2.1557)	-19.95 (± 2.1738)	-12.66 (± 2.1373)	

Statistical analyses

Statistical analysis title	Dapa + Saxa + Met Versus Dapa + Met
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Dapagliflozin + Metformin

Number of subjects included in analysis	562
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0135
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-7.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.59
upper limit	-1.57

Statistical analysis title	Dapa + Saxa + Met Versus Saxa + Met
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Saxagliptin + Metformin
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-14.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.85
upper limit	-8.91

Secondary: Change in total body weight at 24 weeks

End point title	Change in total body weight at 24 weeks[1]

End point description:

To demonstrate the effect of the co-administered saxagliptin 5 mg and dapagliflozin 5 mg to saxagliptin 5 mg on total body weight after 24 weeks. Results were presented for the modified full analysis set. Note: Baseline was defined as the last assessment on or prior to the date of the first dose of the study medication.

End point type	Secondary

End point timeframe:

After week 24

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

End point values	Dapagliflozin + Saxagliptin + Metformin	Saxagliptin + Metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	288		
Units: Kilograms (Kg)				
least squares mean (standard error)	-2.01 (± 0.1829)	-0.41 (± 0.1815)		

Statistical analyses

Statistical analysis title	Dapa + Saxa + Met Versus Saxa + Met
Comparison groups	Dapagliflozin + Saxagliptin + Metformin v Saxagliptin + Metformin
Number of subjects included in analysis	572
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	-1.09

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At enrolment, throughout the treatment period and end of treatment /early termination.

Adverse event reporting additional description:

Adverse event (AE; both serious and non-serious) - undesirable medical condition (symptoms [eg, nausea], signs [eg, tachycardia]/ abnormal investigation results [eg, laboratory findings])/deterioration of pre-existing medical condition following/during exposure to a pharmaceutical product, whether/not considered causally related to the product

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Dapagliflozin + Saxagliptin + Metformin

Reporting group description:

Randomized subjects received orally once daily (QD) dapagliflozin 5 mg and saxagliptin 5 mg film coated tablets as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Saxagliptin + Metformin

Reporting group description:

Randomized subjects received orally QD saxagliptin 5 mg film coated tablet and placebo for dapagliflozin as an add-on to metformin (≥1500 mg/day orally)

Reporting group title	Dapagliflozin + Metformin

Reporting group description:

Randomized subjects received orally QD dapagliflozin 5 mg film coated tablet and placebo for saxagliptin as an add-on to metformin (≥1500 mg/day orally)

Serious adverse events	Dapagliflozin + Saxagliptin + Metformin	Saxagliptin + Metformin	Dapagliflozin + Metformin
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 293 (2.39%)	7 / 295 (2.37%)	8 / 293 (2.73%)
number of deaths (all causes)	1	0	2
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Radius fracture			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteritis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myocardial infarction			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tachycardia			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 293 (0.34%)	0 / 295 (0.00%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Osteomyelitis			

subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 295 (0.34%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 293 (0.00%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Dapagliflozin + Saxagliptin + Metformin	Saxagliptin + Metformin	Dapagliflozin + Metformin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 293 (13.99%)	29 / 295 (9.83%)	39 / 293 (13.31%)
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	12 / 293 (4.10%)	5 / 295 (1.69%)	11 / 293 (3.75%)
occurrences (all)	13	5	11
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 293 (2.05%)	3 / 295 (1.02%)	5 / 293 (1.71%)
occurrences (all)	6	3	5
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	7 / 293 (2.39%)	0 / 295 (0.00%)	1 / 293 (0.34%)
occurrences (all)	8	0	1
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	7 / 293 (2.39%)	5 / 295 (1.69%)	3 / 293 (1.02%)
occurrences (all)	7	5	4
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 293 (1.71%)	8 / 295 (2.71%)	9 / 293 (3.07%)
occurrences (all)	5	8	10
Influenza			
subjects affected / exposed	3 / 293 (1.02%)	3 / 295 (1.02%)	9 / 293 (3.07%)
occurrences (all)	3	3	9
Upper respiratory tract infection			
subjects affected / exposed	3 / 293 (1.02%)	6 / 295 (2.03%)	4 / 293 (1.37%)
occurrences (all)	4	6	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2016	Amendment 1: - Information on ketoacidosis was added to the Benefit/risk and ethical assessment of the clinical study protocol (CSP). - The differentiation between treatment discontinuation from study withdrawal was clarified. - Additional reasons for discontinuation of the study were included in the CSP. - The CSP was clarified with regards to allowing HbA1c re-testing at screening under specific conditions.
18 January 2016	Amendment 2: - Section 3.9.1 was updated to clearly differentiate treatment discontinuation from study withdrawal by removing 'Lost to follow-up' since this was one of the reason for study withdrawal. - The sections on diabetic ketoacidosis (DKA) and DKA adjudication were removed and to be updated after the review from FDA regarding the relevant text to be added in CSP. - Management of maternal exposure cases was clarified. If a subject became pregnant during the course of study all study medication was to be discontinued immediately. Subject was to be continued in the study as per original visit schedule.
04 August 2016	Amendment 3: - Inclusion criteria: FPG criteria were described in mmol/L, and male condom with spermicidal gel was added as an acceptable birth control method. - Exclusion criteria: criterion 8(a) was updated and mentioned as a 8(b) to exclude any exposure of DPP-4 and SGLT-2 inhibitor within 8 weeks prior to enrolment. - Methods for unblinding: pharmacists were removed from the list of persons having access to individual treatment codes. - Study-specific discontinuation criteria: a note was added to withhold study medication when eGFR <60 mL/min/1.73 m2 (by MDRD) until retest eGFR result were available only for randomization visit. – Study Plan: footnote 'k' was added to clarify that rescue medication should also be returned for rescued subjects at Visit 4 & 5. Footnote 'h' was updated to make it clear on pregnancy testing. Visit window for enrolment visit was changed to be consistent with footnote 'c'. Return study medication was added. Study Medication Compliance Review marked for Visit 3. Collect unused study medication/supplies was removed - Enrolment visit: review of the patient diary was removed. - Treatment period visits: provision of patient diary & instructions was removed, and study medication were dispensed and returned at Visit 4. - Description of the time period for collection of AEs: discontinuation visit was deleted. - The reference for the hypoglycaemia classification was updated. - Specific reporting requirements for liver test abnormalities accompanied by jaundice/hyperbilirubinemia, opportunistic infections & severe hypersensitivity were removed. - Treatment compliance evaluation: an upper limit of ≤120% of the prescribed dose was added. - Guidance on management of sustained elevated liver safety abnormalities (CSP Appendix D): a correction was made indicating that subject had to be discontinued from study medication and not from study. - Guidance on actions required in cases of increases in liver biochemistry & evaluation of Hy's Law was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported