



Clinical trial results:

An Exploratory Phase II/III, Randomised, Double-Blind, Placebo Controlled, Parallel Design Study to Evaluate the Efficacy, Safety and Pharmacodynamics of Dapagliflozin and Dapagliflozin in Combination with Saxagliptin in CKD Patients With Type 2 Diabetes Mellitus and Albuminuria Treated with Angiotensin-converting Enzyme Inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB).

Summary

EudraCT number	2015-002676-24
Trial protocol	ES
Global end of trial date	18 May 2018

Results information

Result version number	v1
This version publication date	31 May 2019
First version publication date	31 May 2019

Trial information

Trial identification

Sponsor protocol code	D1690C00023
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02547935
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
Public contact	Global Clinical Lead, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 302 885 1180, 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 May 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine whether dapagliflozin alone or in combination with saxagliptin can decrease albuminuria and improve glycemic control in patients with Type 2 Diabetes Mellitus, albuminuria and renal impairment (Chronic Kidney Disease).

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 for Harmonisation Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 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	Japan: 77
Country: Number of subjects enrolled	Korea, Republic of: 53
Country: Number of subjects enrolled	Taiwan: 36
Country: Number of subjects enrolled	United States: 95
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Mexico: 79
Country: Number of subjects enrolled	South Africa: 42
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	Spain: 24
Worldwide total number of subjects	448
EEA total number of subjects	24

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)	210
From 65 to 84 years	234
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus with micro- or macro-albuminuria and treated with ACEi or ARB were enrolled into an international, multi-centre study from 21 Sep 2015. The last patient's last visit was 18 May 2018.

Pre-assignment

Screening details:

Enrolled patients were screened during a 4-week single-blind placebo lead-in period. Patients who met all of the inclusion and none of the exclusion criteria in this period were eligible to be randomised into the 24-week double-blind placebo-controlled treatment period.

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	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10 mg + Saxagliptin 2.5 mg

Arm description:

Dapagliflozin 10 milligram (mg) and saxagliptin 2.5 mg tablets were taken orally, once daily (in the morning) for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Saxagliptin
Investigational medicinal product code	
Other name	Onglyza™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Saxagliptin 2.5 mg tablet taken orally once a day in the morning for 24 weeks.

Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Forxiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg tablet taken orally once a day in the morning for 24 weeks.

Arm title	Dapagliflozin 10 mg
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Arm description:

Dapagliflozin 10 mg tablets were taken orally, once daily (in the morning) for 24 weeks. Patients also took placebo tablets to match saxagliptin.

Arm type	Experimental
Investigational medicinal product name	Placebo to match saxagliptin 2.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:	
Plcaebo tablet taken orally once a day in the morning for 24 weeks.	
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Forxiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Dapagliflozin 10 mg tablet taken orally once a day in the morning for 24 weeks.	
Arm title	Placebo
Arm description:	
Placebo tablets to match both active products (dapagliflozin and saxagliptin) were taken orally, once daily (in the morning) for 24 weeks.	
Arm type	Placebo
Investigational medicinal product name	Placebo to match dapagliflozin 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Plcaebo tablet taken orally once a day in the morning for 24 weeks.	
Investigational medicinal product name	Placebo to match saxagliptin 2.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Plcaebo tablet taken orally once a day in the morning for 24 weeks.	

Number of subjects in period 1	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo
Started	155	145	148
Received Treatment	152	145	148
Full Analysis Set	152	144	148
Safety Analysis Set	152	145	148
Completed	150	137	143
Not completed	5	8	5
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	2	3	4
Physician decision	-	1	-
Screen Failure	2	-	-
Not specified	-	1	-
Lost to follow-up	-	2	1

Baseline characteristics

Reporting groups

Reporting group title	Dapagliflozin 10 mg + Saxagliptin 2.5 mg
Reporting group description: Dapagliflozin 10 milligram (mg) and saxagliptin 2.5 mg tablets were taken orally, once daily (in the morning) for 24 weeks.	
Reporting group title	Dapagliflozin 10 mg
Reporting group description: Dapagliflozin 10 mg tablets were taken orally, once daily (in the morning) for 24 weeks. Patients also took placebo tablets to match saxagliptin.	
Reporting group title	Placebo
Reporting group description: Placebo tablets to match both active products (dapagliflozin and saxagliptin) were taken orally, once daily (in the morning) for 24 weeks.	

Reporting group values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo
Number of subjects	155	145	148
Age, Customized Units: Subjects			
<65 years	78	64	68
>=65 years	77	81	80
Age Continuous Units: years			
arithmetic mean	64.0	64.7	64.7
standard deviation	± 9.21	± 8.61	± 8.53
Sex: Female, Male Units: Subjects			
Female	45	43	43
Male	110	102	105
Race/Ethnicity, Customized Units: Subjects			
White	77	55	64
Black or African American	8	7	11
Asian	57	67	53
Native Hawaiian or other Pacific Islander	1	2	1
American Indian or Alaska Native	0	1	1
Other	12	13	18
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	42	32	38
Not Hispanic or Latino	113	113	110
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	448		

Age, Customized			
Units: Subjects			
<65 years	210		
>=65 years	238		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	131		
Male	317		
Race/Ethnicity, Customized			
Units: Subjects			
White	196		
Black or African American	26		
Asian	177		
Native Hawaiian or other Pacific Islander	4		
American Indian or Alaska Native	2		
Other	43		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	112		
Not Hispanic or Latino	336		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Dapagliflozin 10 mg + Saxagliptin 2.5 mg
Reporting group description: Dapagliflozin 10 milligram (mg) and saxagliptin 2.5 mg tablets were taken orally, once daily (in the morning) for 24 weeks.	
Reporting group title	Dapagliflozin 10 mg
Reporting group description: Dapagliflozin 10 mg tablets were taken orally, once daily (in the morning) for 24 weeks. Patients also took placebo tablets to match saxagliptin.	
Reporting group title	Placebo
Reporting group description: Placebo tablets to match both active products (dapagliflozin and saxagliptin) were taken orally, once daily (in the morning) for 24 weeks.	

Primary: Adjusted Mean Change from Baseline in Glycosylated Haemoglobin (HbA1c): Comparison of Dapagliflozin 10 mg plus Saxagliptin 2.5 mg and Placebo at Week 24

End point title	Adjusted Mean Change from Baseline in Glycosylated Haemoglobin (HbA1c): Comparison of Dapagliflozin 10 mg plus Saxagliptin 2.5 mg and Placebo at Week 24 ^[1]
End point description: HbA1c was analysed at baseline and every 4 weeks during the 24-week treatment period. Only measurements prior to rescue or treatment discontinuation were analysed. The adjusted mean change from baseline at Week 24 was analysed using a mixed model repeated measures (MMRM) model. Results are presented for patients from the Full Analysis Set (all randomised patients who took at least 1 dose of double-blind study drug and had a non missing baseline value and at least one post-baseline efficacy variable value) and with non-missing baseline and Week 24 values for HbA1c.	
End point type	Primary
End point timeframe: Baseline and 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: This primary endpoint was concerned with comparison of Dapagliflozin 10 mg + Saxagliptin 2.5 mg arm versus placebo only. Comparison of Dapagliflozin 10mg arm to placebo is reported as a secondary endpoint.

End point values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	118		
Units: Percentage				
least squares mean (standard error)	-0.85 (± 0.09)	-0.27 (± 0.09)		

Statistical analyses

Statistical analysis title	Longitudinal Repeated Measures Analysis
Statistical analysis description:	
A longitudinal repeated measures analysis included the fixed categorical effects of treatment, week, randomisation stratification factor (i.e. anti-diabetic treatment strata), and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.	
Comparison groups	Placebo v Dapagliflozin 10 mg + Saxagliptin 2.5 mg
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[2]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[2] - Statistical significance level = 0.025.

Primary: Adjusted Mean Percent Change from Baseline in Urine Albumin-to-Creatinine Ratio (UACR) at Week 24

End point title	Adjusted Mean Percent Change from Baseline in Urine Albumin-to-Creatinine Ratio (UACR) at Week 24
End point description:	
UACR was analysed at baseline and every 4 weeks during the 24-week treatment period. All measurements regardless of rescue medication or treatment discontinuation were analysed. UACR values were first transformed to logarithms and the results were based on exponentiation of model estimates and expressed as adjusted mean percent change from baseline at Week 24. Results are presented for patients from the Full Analysis Set with non-missing baseline and Week 24 values for UACR.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	132	134	
Units: Percentage				
least squares mean (standard error)	-39.1 (± 5.1)	-22.4 (± 6.6)	-1.8 (± 8.3)	

Statistical analyses

Statistical analysis title	Longitudinal Repeated Measures Analysis
Statistical analysis description:	
A longitudinal repeated measures model of the logarithms of the post-baseline to baseline ratios included the fixed categorical effects of treatment, week, treatment-by-week interaction, and randomisation stratification factor (i.e. anti-diabetic treatment strata), as well as the continuous fixed covariates of log-baseline UACR value and log-baseline UACR value-by-week interaction.	
Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 ^[3]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.1
upper limit	-5.2
Variability estimate	Standard error of the mean
Dispersion value	7.3

Notes:

[3] - Statistical significance level = 0.025.

Statistical analysis title	Longitudinal Repeated Measures Analysis
Statistical analysis description:	
A longitudinal repeated measures model of the logarithms of the post-baseline to baseline ratios included the fixed categorical effects of treatment, week, treatment-by-week interaction, and randomisation stratification factor (i.e. anti-diabetic treatment strata), as well as the continuous fixed covariates of log-baseline UACR value and log-baseline UACR value-by-week interaction.	
Comparison groups	Dapagliflozin 10 mg + Saxagliptin 2.5 mg v Placebo
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[4]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.2
upper limit	-25.8
Variability estimate	Standard error of the mean
Dispersion value	5.7

Notes:

[4] - Statistical significance level = 0.025.

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
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End point description:

Total body weight was measured in kilograms (kg) at baseline and at Week 1 then every 4 weeks during the 24-week treatment period. All measurements regardless of rescue medication or treatment discontinuation were analysed. Total body weight values were first transformed to logarithms and the results were based on exponentiation of model estimates and expressed as adjusted mean percent change from baseline at Week 24. Results are presented for patients from the Full Analysis Set with non-missing baseline and Week 24 values for total body weight.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	132	134	
Units: Percentage				
least squares mean (standard error)	-0.65 (± 0.55)	-1.48 (± 0.56)	-0.61 (± 0.56)	

Statistical analyses

Statistical analysis title	Longitudinal Repeated Measures Analysis
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Statistical analysis description:

A longitudinal repeated measures model of the logarithms of the post-baseline to baseline ratios included the fixed categorical effects of treatment, week, treatment-by-week interaction, and randomisation stratification factor (i.e. anti-diabetic treatment strata), as well as the continuous fixed covariates of log-baseline total body weight value and log-baseline total body weight value-by-week interaction.

Comparison groups	Dapagliflozin 10 mg + Saxagliptin 2.5 mg v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.953 ^[5]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	1.26
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[5] - Statistical significance level = 0.025.

Statistical analysis title	Longitudinal Repeated Measures Analysis
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Statistical analysis description:

A longitudinal repeated measures model of the logarithms of the post-baseline to baseline ratios included the fixed categorical effects of treatment, week, treatment-by-week interaction, and randomisation stratification factor (i.e. anti-diabetic treatment strata), as well as the continuous fixed covariates of log-baseline total body weight value and log-baseline total body weight value-by-week interaction.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.193 ^[6]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[6] - Statistical significance level = 0.025.

Secondary: Adjusted Mean Change from Baseline in Fasting Plasma Glucose (FPG) at Week 24

End point title	Adjusted Mean Change from Baseline in Fasting Plasma Glucose (FPG) at Week 24
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End point description:

FPG was analysed at baseline and Week 1 then every 4 weeks during the 24-week treatment period. Only measurements prior to rescue or treatment discontinuation were analysed. The adjusted mean change from baseline at Week 24 was analysed using a MMRM model. Results are presented for patients from the Full Analysis Set with non-missing baseline and Week 24 values for FPG.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136	123	116	
Units: mg/decilitre (dL)				
least squares mean (standard error)	-17.2 (± 5.2)	-13.1 (± 5.4)	-11.2 (± 5.5)	

Statistical analyses

Statistical analysis title	Longitudinal Repeated Measures Analysis
Statistical analysis description:	
A longitudinal repeated measures analysis included the fixed categorical effects of treatment, week, randomisation stratification factor (i.e.anti-diabetic treatment strata), and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.	
Comparison groups	Dapagliflozin 10 mg + Saxagliptin 2.5 mg v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.298 ^[7]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	5.4
Variability estimate	Standard error of the mean
Dispersion value	5.8

Notes:

[7] - Statistical significance level = 0.025.

Statistical analysis title	Longitudinal Repeated Measures Analysis
Statistical analysis description:	
A longitudinal repeated measures analysis included the fixed categorical effects of treatment, week, randomisation stratification factor (i.e.anti-diabetic treatment strata), and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.	
Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746 ^[8]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	9.8
Variability estimate	Standard error of the mean
Dispersion value	5.9

Notes:

[8] - Statistical significance level = 0.025.

Secondary: Percentage of Patients Achieving at Least 30% Reduction in UACR at Week 24

End point title	Percentage of Patients Achieving at Least 30% Reduction in UACR at Week 24
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End point description:

The proportion of responders (i.e. percentage of patients meeting the criteria of at least a 30% reduction in UACR), was analysed using a logistic regression model. If no measurement was available at Week 24 the last available post-baseline measurement was carried forward (Last Observation Carried Forward [LOCF]). Results are presented for patients from the Full Analysis Set with non-missing baseline and at least one post-baseline UACR value.

End point type	Secondary
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End point timeframe:

From baseline up to Week 24

End point values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	140	144	
Units: Percentage				
number (not applicable)	57.0	45.0	31.3	

Statistical analyses

Statistical analysis title	Logistic Regression Model Analysis
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Statistical analysis description:

Logistic regression model analysis with adjustment for baseline UACR and pooled randomisation strata.

Comparison groups	Dapagliflozin 10 mg + Saxagliptin 2.5 mg v Placebo
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Number of subjects included in analysis	295
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.001 ^[9]
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Method	Regression, Logistic
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Parameter estimate	Odds ratio (OR)
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Point estimate	2.98
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	1.8
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upper limit	4.8
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Notes:

[9] - Statistical significance level = 0.025.

Statistical analysis title	Logistic Regression Model Analysis
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Statistical analysis description:

Logistic regression model analysis with adjustment for baseline UACR and pooled randomisation strata.

Comparison groups	Dapagliflozin 10 mg v Placebo
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Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 ^[10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3

Notes:

[10] - Statistical significance level = 0.025.

Secondary: Percentage of Patients Achieving a Reduction in HbA1c of Less than 7.0% at Week 24

End point title	Percentage of Patients Achieving a Reduction in HbA1c of Less than 7.0% at Week 24
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End point description:

The proportion of responders (i.e. percentage of patients meeting the criteria of a less than 7% reduction in HbA1c), was analysed using a logistic regression model. If no measurement was available at Week 24 the last available post-baseline measurement was carried forward (LOCF). Only measurements prior to rescue or treatment discontinuation were analysed. Results are presented for patients from the Full Analysis Set with non-missing baseline and at least one post-baseline HbA1c value.

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	140	145	
Units: Percentage				
number (not applicable)	35.1	15.0	10.3	

Statistical analyses

Statistical analysis title	Logistic Regression Model Analysis
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Statistical analysis description:

Logistic regression model analysis with adjustment for baseline HbA1c and pooled randomisation strata.

Comparison groups	Dapagliflozin 10 mg + Saxagliptin 2.5 mg v Placebo
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Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[11]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	11.2

Notes:

[11] - Statistical significance level = 0.025.

Statistical analysis title	Logistic Regression Model Analysis
Statistical analysis description:	
Logistic regression model analysis with adjustment for baseline HbA1c and pooled randomisation strata.	
Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167 ^[12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	3.8

Notes:

[12] - Statistical significance level = 0.025.

Secondary: Adjusted Mean Change from Baseline in Seated Systolic Blood Pressure (SBP) at Week 24

End point title	Adjusted Mean Change from Baseline in Seated Systolic Blood Pressure (SBP) at Week 24
End point description:	
Seated SBP was analysed at baseline, Week 1 and every 4 weeks during the 24-week treatment period. All measurements regardless of rescue medication or treatment discontinuation were analysed. The adjusted mean change from baseline at Week 24 was analysed using a MMRM model. Results are presented for patients from the Full Analysis Set with non-missing baseline and Week 24 values for SBP.	
End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Dapagliflozin 10 mg + Saxagliptin 2.5 mg	Dapagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	132	134	
Units: Millimetre of mercury (mmHg)				
least squares mean (standard error)	-8.8 (± 1.6)	-6.9 (± 1.7)	-4.1 (± 1.7)	

Statistical analyses

Statistical analysis title	Longitudinal Repeated Measures Analysis
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Statistical analysis description:

A longitudinal repeated measures model of the logarithms of the post-baseline to baseline ratios, included the fixed categorical effects of treatment, week, treatment-by-week interaction, and randomisation strata, as well as the continuous fixed covariates of log-baseline SBP value and log-baseline SBP value-by-week interaction.

Comparison groups	Dapagliflozin 10 mg v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.122 ^[13]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	1.8

Notes:

[13] - Statistical significance level = 0.025.

Statistical analysis title	Longitudinal Repeated Measures Analysis
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Statistical analysis description:

A longitudinal repeated measures model of the logarithms of the post-baseline to baseline ratios, included the fixed categorical effects of treatment, week, treatment-by-week interaction, and randomisation strata, as well as the continuous fixed covariates of log-baseline SBP value and log-baseline SBP value-by-week interaction.

Comparison groups	Dapagliflozin 10 mg + Saxagliptin 2.5 mg v Placebo
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 ^[14]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-4.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	-1.2
Variability estimate	Standard error of the mean
Dispersion value	1.8

Notes:

[14] - Statistical significance level = 0.025.

Secondary: Adjusted Mean Change from Baseline in HbA1c: Comparison of Dapagliflozin 10 mg and Placebo at Week 24

End point title	Adjusted Mean Change from Baseline in HbA1c: Comparison of Dapagliflozin 10 mg and Placebo at Week 24 ^[15]
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End point description:

HbA1c was analysed at baseline and every 4 weeks during the 24-week treatment period. Only measurements prior to rescue or treatment discontinuation were analysed. The adjusted mean change from baseline at Week 24 was analysed using a MMRM model. Results are presented for patients from the Full Analysis Set with non-missing baseline and Week 24 values for HbA1c.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

Notes:

[15] - 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: This secondary endpoint was concerned with comparison of Dapagliflozin 10 mg arm versus placebo only. Comparison of Dapagliflozin 10 + Saxagliptin 2.5 mg arm to placebo is reported as a primary endpoint.

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	118		
Units: Percentage				
least squares mean (standard error)	-0.43 (± 0.09)	-0.27 (± 0.09)		

Statistical analyses

Statistical analysis title	Longitudinal Repeated Measures Analysis
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Statistical analysis description:

A longitudinal repeated measures analysis included the fixed categorical effects of treatment, week, randomisation stratification factor (i.e. anti-diabetic treatment strata), and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

Comparison groups	Dapagliflozin 10 mg v Placebo
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Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142 ^[16]
Method	MMRM
Parameter estimate	Difference in adjusted mean change
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[16] - Statistical significance level = 0.025.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events (AEs) were reported from Day 1 until the last day of double-blind treatment +4 days. Serious AEs were included up to the last day of double-blind treatment + 30 days. A total maximum time frame of 28 weeks.

Adverse event reporting additional description:

The Safety Analysis Set consisted of all patients who received at least 1 dose of study drug during the 24-week double-blind treatment period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Dapagliflozin 10 mg
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Reporting group description:

Dapagliflozin 10 mg tablets were taken orally, once daily (in the morning) for 24 weeks. Patients also took placebo tablets to match saxagliptin.

Reporting group title	Placebo
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Reporting group description:

Placebo tablets to match both active products (dapagliflozin and saxagliptin) were taken orally, once daily (in the morning) for 24 weeks.

Reporting group title	Dapagliflozin 10 mg + Saxagliptin 2.5 mg
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Reporting group description:

Dapagliflozin 10 mg and saxagliptin 2.5 mg tablets were taken orally, once daily (in the morning) for 24 weeks.

Serious adverse events	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg + Saxagliptin 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 145 (8.28%)	16 / 148 (10.81%)	12 / 152 (7.89%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	1	0	1
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 145 (0.00%)	2 / 148 (1.35%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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 pectoris			
subjects affected / exposed	1 / 145 (0.69%)	2 / 148 (1.35%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 145 (0.00%)	2 / 148 (1.35%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 145 (0.00%)	2 / 148 (1.35%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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
Headache			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Presyncope			

subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Syncope			
subjects affected / exposed	2 / 145 (1.38%)	0 / 148 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Iron deficiency anaemia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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

Duodenal ulcer haemorrhage subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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
Skin and subcutaneous tissue disorders			
Diabetic foot subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed	0 / 145 (0.00%)	2 / 148 (1.35%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerulonephritis rapidly progressive			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Urinary retention			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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
Infections and infestations			
Diabetic foot infection			

subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysematous pyelonephritis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	0 / 145 (0.00%)	0 / 148 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (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
Urinary tract infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 148 (0.00%)	0 / 152 (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
Hypoglycaemia			

subjects affected / exposed	0 / 145 (0.00%)	1 / 148 (0.68%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg + Saxagliptin 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 145 (12.41%)	8 / 148 (5.41%)	12 / 152 (7.89%)
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 145 (5.52%)	2 / 148 (1.35%)	2 / 152 (1.32%)
occurrences (all)	8	2	2
Nasopharyngitis			
subjects affected / exposed	10 / 145 (6.90%)	6 / 148 (4.05%)	10 / 152 (6.58%)
occurrences (all)	11	6	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2015	Major changes included: Benefit/risk and overdose text revised to align with new Investigator Brochure. Added additional 24 hour laboratory assessments. Revised allowed concomitant medication text to specify that doses should remain constant throughout both the 24-week treatment period and the 3 week follow-up period. Increased upper Body Mass Index limit in inclusion criteria from 40 kg/m2 to 45 kg/m2. 24 hour urine assessments were removed from Visits 5 and 7.
08 January 2016	Major changes included: added measurement of arterial stiffness in Canada, Spain & US to Exploratory Objectives listed for both the Saxagliptin/Dapagliflozin and Dapagliflozin treatment arms. Exclusion criteria section was changed to patients with Type 1 Diabetes Mellitus, history of pancreatitis or pancreatic surgery. Benefit/risk section was modified to add new text regarding risk of ketoacidosis.
01 April 2016	Major changes included: AEs of special interest section was updated to include regulatory requirements. The HbA1c and estimated glomerular filtration rate (eGFR) limits and the insulin regimen were updated due to modification of inclusion criteria. Lost to follow-up was added as one of the withdrawal criteria from the study due to comment from FDA. The concomitant and other treatments section was updated to allow use of erythropoiesis stimulating agents with restrictions due to modification of exclusion criteria. Analysis of the secondary variables and Exploratory analysis updated to replace current methodology with a logistic regression model.
17 November 2016	Major changes included: eGFR limits were updated. The target patient population has been changed to Chronic Kidney Disease patients with Type 2 Diabetes Mellitus and albuminuria, due to modification of eGFR inclusion criteria. Concomitant and other treatments section modified to remove the anaemia treatment from the list of prohibited medication. AEs of special interest section removed.
18 September 2017	Major changes included: information related to the reporting and adjudication of diabetic ketoacidosis events in the study. New section added to describe collection of specific information related to AEs leading to amputation and AEs leading to a risk for lower limb amputations in globally sponsored dapagliflozin studies.

Notes:

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.

Anomalous data at 1 site was identified following completion of the study. All data from this site were excluded from the full analysis following an audit; the findings led the sponsor to believe the site did not comply with the principles of GCP.

Notes: