



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 | v2 (current) |
| This version publication date | 04 October 2019 |
| First version publication date | 31 May 2019 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D1690C00023 |
|-----------------------|-------------|

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 | 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.

| | |
|--|--------------------|
| 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.

| | |
|------------------|---------------------|
| Arm title | Dapagliflozin 10 mg |
|------------------|---------------------|

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: The primary endpoint was concerned with comparison of Dapagliflozin 10 mg + Saxagliptin 2.5 mg arm versus placebo only. Comparison of Dapagliflozin 10 mg 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 of Glycosylated HbA1c | | | | |
| 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 | Dapagliflozin 10 mg + Saxagliptin 2.5 mg v Placebo |
| 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: Percent change | | | | |
| 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 + Saxagliptin 2.5 mg v Placebo |
| Number of subjects included in analysis | 273 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[3] |
| 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:

[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 v Placebo |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.011 ^[4] |
| 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:

[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 |
|-----------------|--|

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 |
|----------------|-----------|

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: Percent change | | | | |
| 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 |
|----------------------------|---|

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 |
|----------------------------|---|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

End point description:

The 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 |
|----------------|-----------|

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 of patients | | | | |
| number (not applicable) | 57.0 | 45.0 | 31.3 | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Logistic Regression Model Analysis |
|----------------------------|------------------------------------|

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 |
|-------------------|--|

| | |
|---|-----|
| Number of subjects included in analysis | 295 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|------------------------|
| P-value | < 0.001 ^[9] |
|---------|------------------------|

| | |
|--------|----------------------|
| Method | Regression, Logistic |
|--------|----------------------|

| | |
|--------------------|-----------------|
| Parameter estimate | Odds ratio (OR) |
|--------------------|-----------------|

| | |
|----------------|------|
| Point estimate | 2.98 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|-----|
| lower limit | 1.8 |
|-------------|-----|

| | |
|-------------|-----|
| upper limit | 4.8 |
|-------------|-----|

Notes:

[9] - Statistical significance level = 0.025.

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Logistic Regression Model Analysis |
|----------------------------|------------------------------------|

Statistical analysis description:

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

| | |
|-------------------|-------------------------------|
| Comparison groups | Dapagliflozin 10 mg v Placebo |
|-------------------|-------------------------------|

| | |
|---|-------------------------|
| 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 |
|-----------------|--|

End point description:

The 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 |
|----------------|-----------|

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 of patients | | | | |
| number (not applicable) | 35.1 | 15.0 | 10.3 | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| 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 + Saxagliptin 2.5 mg v Placebo |
|-------------------|--|

| | |
|---|-------------------------|
| 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 |
|----------------------------|---|
|----------------------------|---|

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 ^[13] |
| 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:

[13] - 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 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 ^[14] |
| 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:

[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] |
|-----------------|---|

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 |
|----------------|-----------|

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 mg + Saxagliptin 2.5 mg arm to placebo is reported as the primary endpoint.

| End point values | Dapagliflozin 10 mg | Placebo | | |
|---|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 118 | | |
| Units: Percentage of Glycosylated HbA1c | | | | |
| least squares mean (standard error) | -0.43 (± 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 | Dapagliflozin 10 mg v Placebo |
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| 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 title | Dapagliflozin 10 mg + Saxagliptin 2.5 mg |
|-----------------------|--|

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 | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 145 (6.90%) | 6 / 148 (4.05%) | 10 / 152 (6.58%) |
| occurrences (all) | 11 | 6 | 12 |
| Influenza | | | |
| subjects affected / exposed | 8 / 145 (5.52%) | 2 / 148 (1.35%) | 2 / 152 (1.32%) |
| occurrences (all) | 8 | 2 | 2 |

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: