



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D1690C00024 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Global Clinical Leader-Dapagliflozin AstraZeneca |
| Sponsor organisation address | Pepparedsleden 1, Mölndal, Sweden, SE-431 83 |
| Public contact | Anna Maria Langkilde, MD PhD, Global Clinical Leader-Dapagliflozin AstraZeneca, +46 31 776 1000, information.center@astrazeneca.com |
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Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 07 March 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 November 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 15 June 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Bulgaria: 53 |
| Country: Number of subjects enrolled | Czech Republic: 22 |
| Country: Number of subjects enrolled | Italy: 28 |
| Country: Number of subjects enrolled | Poland: 29 |
| Country: Number of subjects enrolled | Spain: 46 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Canada: 49 |
| Country: Number of subjects enrolled | United States: 91 |

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

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 110 |
| From 65 to 84 years | 211 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Arms

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

Arm description:

10 mg Tablets, Oral, Once daily, 24 weeks

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

Dosage and administration details:

Dapagliflozin 10mg QD

| | |
|------------------|------------|
| Arm title | Placebo QD |
|------------------|------------|

Arm description:

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

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

Dosage and administration details:

Placebo QD

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Dapagliflozin 10mg QD |
|-----------------------|-----------------------|

Reporting group description:

10 mg Tablets, Oral, Once daily, 24 weeks

| | |
|-----------------------|------------|
| Reporting group title | Placebo QD |
|-----------------------|------------|

Reporting group description:

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

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

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

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

Statistical analyses

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

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

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

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

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

Statistical analyses

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

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.15 |

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

| | |
|-----------------|--|
| End point title | Adjusted mean change from baseline in seated SBP at Week 24. |
|-----------------|--|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Week 24

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

Statistical analyses

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | SBP change from baseline to Week 24 |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

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

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

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Dapagliflozin 10mg QD |
|-----------------------|-----------------------|

Reporting group description:

10 mg Tablets, Oral, Once daily, 24 weeks

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported