



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, 3-arm, Parallel-group 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment who have Inadequate Glycemic Control

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2016-004889-26 |
| Trial protocol | ES DE HU IT RO |
| Global end of trial date | 25 October 2019 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 20 September 2020 |
| First version publication date | 20 September 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC14837 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03242252 |
| WHO universal trial number (UTN) | U1111-1187-8662 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Lexicon Pharmaceuticals, Inc. |
| Sponsor organisation address | 8800 Technology Forest Place, The Woodlands, United States, TX 77381 |
| Public contact | Medical Affairs, Lexicon Pharmaceuticals, Inc., medical-information@lexpharma.com |
| Scientific contact | Medical Affairs, Lexicon Pharmaceuticals, Inc., medical-information@lexpharma.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 | 25 October 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of sotagliflozin 200 milligrams (mg) and sotagliflozin 400 mg versus placebo on hemoglobin A1c (HbA1c) reduction at Week 26 in subjects with Type 2 diabetes who have inadequate glycemic control and moderate renal impairment.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 16 August 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 84 |
| Country: Number of subjects enrolled | Spain: 34 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Hungary: 57 |
| Country: Number of subjects enrolled | Argentina: 24 |
| Country: Number of subjects enrolled | Brazil: 66 |
| Country: Number of subjects enrolled | Canada: 41 |
| Country: Number of subjects enrolled | Colombia: 32 |
| Country: Number of subjects enrolled | Israel: 56 |
| Country: Number of subjects enrolled | Italy: 19 |
| Country: Number of subjects enrolled | Mexico: 34 |
| Country: Number of subjects enrolled | Romania: 33 |
| Country: Number of subjects enrolled | Russian Federation: 39 |
| Country: Number of subjects enrolled | South Africa: 22 |
| Country: Number of subjects enrolled | Ukraine: 39 |
| Country: Number of subjects enrolled | United States: 200 |
| Worldwide total number of subjects | 787 |
| EEA total number of subjects | 234 |

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) | 197 |
| From 65 to 84 years | 576 |
| 85 years and over | 14 |

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 166 investigative sites in the United States, Argentina, Brazil, Canada, Colombia, Germany, Hungary, Israel, Italy, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, and Ukraine from 16 August 2017 to 25 October 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of Type 2 Diabetes Mellitus were enrolled in 1 of 3 treatment groups: Placebo or Sotagliflozin 200 mg or Sotagliflozin 400 mg. Subjects were randomly assigned in the ratio of 1:1:1 to these reporting groups.

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, Carer |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 54 weeks.

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

Dosage and administration details:

Placebo was administered as two tablets (identical to sotagliflozin in appearance), once daily before the first meal of the day.

| | |
|------------------|----------------------|
| Arm title | Sotagliflozin 200 mg |
|------------------|----------------------|

Arm description:

Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks.

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

Dosage and administration details:

Placebo was administered as one tablet (identical to the sotagliflozin 200 mg tablet in appearance), orally, once daily before the first meal of the day.

| | |
|--|---------------|
| Investigational medicinal product name | Sotagliflozin |
| Investigational medicinal product code | |
| Other name | SAR439954 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Sotagliflozin 200 mg was administered as one tablet, orally once daily before the first meal of the day.

| | |
|--|----------------------|
| Arm title | Sotagliflozin 400 mg |
| Arm description: Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | Sotagliflozin |
| Investigational medicinal product code | |
| Other name | SAR439954 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Sotagliflozin 400 mg was administered as two sotagliflozin 200 mg tablets, orally once daily before the first meal of the day.

| Number of subjects in period 1 | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg |
|---------------------------------------|---------|----------------------|----------------------|
| Started | 260 | 263 | 264 |
| Completed | 224 | 240 | 232 |
| Not completed | 36 | 23 | 32 |
| At the subject's own request | 18 | 10 | 15 |
| Adverse event | 8 | 6 | 9 |
| Study terminated by sponsor | 1 | - | - |
| Poor compliance to protocol | - | 2 | 3 |
| Lost to follow-up | 5 | 1 | 4 |
| Reason not specified | 4 | 4 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|----------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 54 weeks. | |
| Reporting group title | Sotagliflozin 200 mg |
| Reporting group description: | |
| Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks. | |
| Reporting group title | Sotagliflozin 400 mg |
| Reporting group description: | |
| Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks. | |

| Reporting group values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg |
|------------------------|---------|----------------------|----------------------|
| Number of subjects | 260 | 263 | 264 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|--------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 69.3 | 69.6 | 69.5 |
| standard deviation | ± 8.1 | ± 7.5 | ± 8.2 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 111 | 120 | 112 |
| Male | 149 | 143 | 152 |
| Race | | | |
| Units: Subjects | | | |
| White | 220 | 231 | 215 |
| Black or African American | 12 | 14 | 15 |
| Asian | 5 | 7 | 8 |
| American Indian or Alaska Native | 15 | 9 | 20 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 |
| Multiple | 3 | 0 | 3 |
| Not Reported | 2 | 0 | 3 |
| Unknown | 2 | 1 | 0 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 67 | 67 | 64 |
| Not Hispanic or Latino | 193 | 196 | 200 |
| HbA1c | | | |
| Units: percentage of HbA1c | | | |
| arithmetic mean | 8.33 | 8.33 | 8.31 |
| standard deviation | ± 1.00 | ± 0.90 | ± 0.94 |
| Systolic Blood Pressure (SBP) | | | |
| Units: millimetre of mercury (mmHg) | | | |

| | | | |
|--------------------|---------|---------|---------|
| arithmetic mean | 140.59 | 140.31 | 141.71 |
| standard deviation | ± 14.59 | ± 15.15 | ± 15.01 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 787 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|-----|--|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 343 | | |
| Male | 444 | | |
| Race | | | |
| Units: Subjects | | | |
| White | 666 | | |
| Black or African American | 41 | | |
| Asian | 20 | | |
| American Indian or Alaska Native | 44 | | |
| Native Hawaiian or Other Pacific Islander | 2 | | |
| Multiple | 6 | | |
| Not Reported | 5 | | |
| Unknown | 3 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 198 | | |
| Not Hispanic or Latino | 589 | | |
| HbA1c | | | |
| Units: percentage of HbA1c | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Systolic Blood Pressure (SBP) | | | |
| Units: millimetre of mercury (mmHg) | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|--|----------------------|
| Reporting group title | Placebo |
| Reporting group description: Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 54 weeks. | |
| Reporting group title | Sotagliflozin 200 mg |
| Reporting group description: Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks. | |
| Reporting group title | Sotagliflozin 400 mg |
| Reporting group description: Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks. | |
| Subject analysis set title | Sotagliflozin 200 mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks. Four subjects randomised to sotagliflozin 400 mg were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg were included in the sotagliflozin 200 mg arm in the safety population. | |
| Subject analysis set title | Sotagliflozin 400 mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks. Four subjects randomised to sotagliflozin 400 mg were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg were included in the sotagliflozin 200 mg arm in the safety population. | |

Primary: Change From Baseline in HbA1c % at Week 26

| | |
|--|--|
| End point title | Change From Baseline in HbA1c % at Week 26 |
| End point description: An Analysis of covariance (ANCOVA) model was used for analysis. Intent-to-treat (ITT) population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using control-based copy reference multiple imputation under the missing not at random framework. | |
| End point type | Primary |
| End point timeframe: Baseline to Week 26 | |

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 260 | 263 | 264 | |
| Units: percentage of HbA1c | | | | |
| least squares mean (standard error) | -0.22 (± 0.061) | -0.32 (± 0.060) | -0.46 (± 0.060) | |

Statistical analyses

| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
|--|---------------------------------------|
| Statistical analysis description: | |
| The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of Chronic Kidney Disease (CKD) stage (3A, 3B) at screening, and country as fixed effects, and baseline HbA1c as a covariate. | |
| Comparison groups | Placebo v Sotagliflozin 200 mg |
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2095 |
| Method | ANCOVA |
| Parameter estimate | Difference in Least Square (LS) Means |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.245 |
| upper limit | 0.054 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.076 |

| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
|---|---------------------------------|
| Statistical analysis description: | |
| The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline HbA1c as a covariate. | |
| Comparison groups | Placebo v Sotagliflozin 400 mg |
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0021 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.386 |
| upper limit | -0.085 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.077 |

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Week 26

| | |
|-----------------|---|
| End point title | Change From Baseline in Fasting Plasma Glucose (FPG) at Week 26 |
|-----------------|---|

End point description:

An ANCOVA model was used for analysis. ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 26 | |

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 260 | 263 | 264 | |
| Units: millimole per litre (mmol/L) | | | | |
| least squares mean (standard error) | -0.374 (\pm 0.1949) | -0.961 (\pm 0.1715) | -0.852 (\pm 0.1668) | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
|----------------------------|---------------------------------|

Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline FPG as a covariate.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Sotagliflozin 200 mg |
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0144 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.587 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.0564 |
| upper limit | -0.1169 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2397 |

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
|----------------------------|---------------------------------|

Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline FPG as a covariate.

| | |
|-------------------|--------------------------------|
| Comparison groups | Placebo v Sotagliflozin 400 mg |
|-------------------|--------------------------------|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0436 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.478 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.942 |
| upper limit | -0.0136 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2368 |

Secondary: Change From Baseline in SBP for Subjects With Baseline SBP ≥ 130 mmHg at Week 12

| | |
|------------------------|--|
| End point title | Change From Baseline in SBP for Subjects With Baseline SBP ≥ 130 mmHg at Week 12 |
| End point description: | An ANCOVA model was used for analysis. Analysis population included subjects with baseline SBP ≥ 130 mmHg in ITT population where, ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method. |
| End point type | Secondary |
| End point timeframe: | Baseline to Week 12 |

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 175 | 162 | 182 | |
| Units: millimetre of mercury (mmHg) | | | | |
| least squares mean (standard error) | -5.18 (\pm 1.462) | -7.46 (\pm 1.597) | -7.71 (\pm 1.247) | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
| Statistical analysis description: | The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline SBP as a covariate. |
| Comparison groups | Placebo v Sotagliflozin 200 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 337 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2627 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -2.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.265 |
| upper limit | 1.709 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.034 |

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, and country as fixed effects, and baseline SBP as a covariate.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Sotagliflozin 400 mg |
| Number of subjects included in analysis | 357 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1602 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -2.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.052 |
| upper limit | 1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.799 |

Secondary: Change From Baseline in SBP at Week 12 for All Subjects

| | |
|-----------------|---|
| End point title | Change From Baseline in SBP at Week 12 for All Subjects |
|-----------------|---|

End point description:

An ANCOVA model was used for analysis. ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method.

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

End point timeframe:

Baseline to Week 12

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 260 | 263 | 264 | |
| Units: mmHg | | | | |
| least squares mean (standard error) | -3.31 (\pm 1.037) | -4.91 (\pm 1.010) | -4.94 (\pm 0.983) | |

Statistical analyses

| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
|---|---------------------------------|
| Statistical analysis description: | |
| The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline SBP as a covariate. | |
| Comparison groups | Placebo v Sotagliflozin 200 mg |
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2212 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.142 |
| upper limit | 0.958 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.301 |

| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
|---|---------------------------------|
| Statistical analysis description: | |
| The change from baseline to Week 12 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline SBP as a covariate. | |
| Comparison groups | Placebo v Sotagliflozin 400 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2089 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.171 |
| upper limit | 0.912 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.297 |

Secondary: Change From Baseline in Body Weight at Week 26

| | |
|---|--|
| End point title | Change From Baseline in Body Weight at Week 26 |
| End point description: An ANCOVA model was used for analysis. ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using the retrieved dropouts & washout imputation method. | |
| End point type | Secondary |
| End point timeframe: Baseline to Week 26 | |

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 260 | 263 | 264 | |
| Units: kilogram (kg) | | | | |
| least squares mean (standard error) | -0.38 (± 0.262) | -1.66 (± 0.246) | -1.20 (± 0.257) | |

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
| Statistical analysis description: The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline body weight as a covariate. | |
| Comparison groups | Placebo v Sotagliflozin 200 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.92 |
| upper limit | -0.644 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.326 |

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and baseline body weight as a covariate.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Sotagliflozin 400 mg |
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0155 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.487 |
| upper limit | -0.156 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.339 |

Secondary: Percentage Change from Baseline in the Urine Albumin: Creatinine Ratio (UACR) at Week 26 in Subjects with Baseline UACR >30 milligrams per gram (mg/g)

| | |
|-----------------|--|
| End point title | Percentage Change from Baseline in the Urine Albumin: Creatinine Ratio (UACR) at Week 26 in Subjects with Baseline UACR >30 milligrams per gram (mg/g) |
|-----------------|--|

End point description:

An ANCOVA model was used for analysis. Analysis population included subjects with baseline UACR > 30 mg/g in ITT population where, ITT population included all randomised subjects or subjects analysed according to their randomised treatment. Missing data was imputed using control-based copy reference multiple imputation under the missing not at random framework.

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

End point timeframe:

Baseline to Week 26

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-----------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 260 | 263 | 264 | |
| Units: percent change | | | | |
| number (not applicable) | -18.71 | -43.68 | -48.12 | |

Statistical analyses

| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
|----------------------------|---------------------------------|
|----------------------------|---------------------------------|

Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and and log-transformed baseline UACR as a covariate.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Sotagliflozin 200 mg |
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0015 |
| Method | ANCOVA |
| Parameter estimate | Percent Difference |
| Point estimate | -30.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -44.78 |
| upper limit | -13.07 |

| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
|----------------------------|---------------------------------|
|----------------------------|---------------------------------|

Statistical analysis description:

The change from baseline to Week 26 was analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening, randomisation stratum of CKD stage (3A, 3B) at screening, country as fixed effects, and and log-transformed baseline UACR as a covariate.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Sotagliflozin 400 mg |
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 |
| Method | ANCOVA |
| Parameter estimate | Percent Difference |
| Point estimate | -36.18 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -49.91 |
| upper limit | -18.68 |

Secondary: Percentage of Subjects With HbA1c < 6.5% at Week 26

| | |
|---|---|
| End point title | Percentage of Subjects With HbA1c < 6.5% at Week 26 |
| End point description: ITT population included all randomised subjects or subjects analysed according to their randomised treatment. | |
| End point type | Secondary |
| End point timeframe: Week 26 | |

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 260 | 263 | 264 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 4.2 | 5.7 | 5.7 | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
| Statistical analysis description: Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening. | |
| Comparison groups | Placebo v Sotagliflozin 200 mg |
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4328 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.23 |
| upper limit | 5.21 |

| | |
|---|---------------------------------|
| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
| Statistical analysis description: Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening. | |
| Comparison groups | Placebo v Sotagliflozin 400 mg |
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4328 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 5.17 |

Secondary: Percentage of Subjects with HbA1c < 7.0% at Week 26

| | |
|---|---|
| End point title | Percentage of Subjects with HbA1c < 7.0% at Week 26 |
| End point description: ITT population included all randomised subjects or subjects analysed according to their randomised treatment. | |
| End point type | Secondary |
| End point timeframe: Week 26 | |

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 260 | 263 | 264 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 13.5 | 19.4 | 20.8 | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Sotagliflozin 200 mg Vs Placebo |
| Statistical analysis description: Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening. | |
| Comparison groups | Placebo v Sotagliflozin 200 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 523 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0614 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 12.21 |

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Sotagliflozin 400 mg Vs Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.5 , $> 8.5\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening and randomisation strata of CKD stage (3A, 3B) at screening.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Sotagliflozin 400 mg |
| Number of subjects included in analysis | 524 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.023 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 7.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.08 |
| upper limit | 13.65 |

Secondary: Percentage of Subjects With Treatment-emergent Adverse Events (TEAEs)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Treatment-emergent Adverse Events (TEAEs) ^[1] |
|-----------------|--|

End point description:

Safety population included all subjects who received at least 1 dose of study drug analysed according to the treatment actually received.

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

End point timeframe:

Up to 60 weeks

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 endpoint was planned to be reported for the following reporting arms Placebo and subject analysis sets Sotagliflozin 200 mg and Sotagliflozin 400 mg.

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|-------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 260 | 267 | 260 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 78.1 | 76.8 | 74.2 | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects with Hypoglycemic Events

| | |
|-----------------|--|
| End point title | Percentage of Subjects with Hypoglycemic Events ^[2] |
|-----------------|--|

End point description:

Percentage of subjects with hypoglycemic events are reported for the following 3 categories: Any hypoglycemia (as reported in the Electronic Case Report Form); Documented symptomatic hypoglycemia [typical symptoms of hypoglycemia (increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, and/or coma) and plasma glucose \leq 70 mg/dL (3.9 mmol/L)]; Severe [an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose or other resuscitative actions] or documented symptomatic hypoglycemia [typical symptoms of hypoglycemia and plasma glucose \leq 70 mg/dL]. Safety population included all subjects who received at least 1 dose of study drug analysed according to the treatment actually received.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 60 weeks

Notes:

[2] - 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 endpoint was planned to be reported for the following reporting arms Placebo and subject analysis sets Sotagliflozin 200 mg and Sotagliflozin 400 mg.

| End point values | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg | |
|---|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 260 | 267 | 260 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Any hypoglycemia | 38.1 | 41.9 | 35.4 | |
| Documented symptomatic hypoglycemia | 26.9 | 29.6 | 22.3 | |
| Severe or documented symptomatic hypoglycemia | 26.9 | 29.6 | 22.3 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 60 weeks

Adverse event reporting additional description:

Safety population included all subjects who received at least 1 dose of study drug analysed according to the treatment actually received. Hypoglycemia was captured and handled separately from other adverse events and is reported in the endpoint section.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Following a 2-week run-in phase, subjects received two placebo tablets (identical to sotagliflozin 200 mg in appearance) orally once daily for up to 54 weeks.

| | |
|-----------------------|----------------------|
| Reporting group title | Sotagliflozin 200 mg |
|-----------------------|----------------------|

Reporting group description:

Following a 2-week run-in phase, subjects received two tablets, one sotagliflozin 200 mg tablet and one placebo tablet (identical to sotagliflozin 200 mg in appearance), orally once daily for up to 58 weeks. Four subjects randomised to sotagliflozin 400 mg were dosed with both sotagliflozin 200 mg and sotagliflozin 400 mg were included in the sotagliflozin 200 mg arm in the safety population.

| | |
|-----------------------|----------------------|
| Reporting group title | Sotagliflozin 400 mg |
|-----------------------|----------------------|

Reporting group description:

Following a 2-week run-in phase, subjects received sotagliflozin 400 mg, administered as two sotagliflozin 200 mg tablets, orally once daily for up to 60 weeks.

| Serious adverse events | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg |
|---|-------------------|----------------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 48 / 260 (18.46%) | 43 / 267 (16.10%) | 44 / 260 (16.92%) |
| number of deaths (all causes) | 3 | 2 | 5 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Breast cancer | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Breast cancer female | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Lipoma | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Malignant melanoma of eyelid | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Uterine neoplasm | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral artery aneurysm | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Peripheral artery stenosis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 267 (0.75%) | 0 / 260 (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 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Cardiac death | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Vocal cord polyp | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Panic attack | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Investigations | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cranio-cerebral injury | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Procedural shock | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 2 / 267 (0.75%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 4 / 267 (1.50%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 arrest | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 failure acute | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 failure chronic | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | 3 / 260 (1.15%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Basal ganglia infarction | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 3 / 267 (1.12%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolic stroke | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Hypoglycaemic unconsciousness | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 267 (0.75%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 2 / 267 (0.75%) | 0 / 260 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Iris neovascularisation | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 267 (0.75%) | 0 / 260 (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 |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Mallory-Weiss syndrome | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Liver injury | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 ulcer | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| 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 / 260 (0.00%) | 0 / 267 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| End stage renal disease | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 | | | |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 1 / 267 (0.37%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tenosynovitis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 267 (0.75%) | 0 / 260 (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 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Corneal abscess | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Enterococcal infection | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Funguria | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Gangrene | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Infective periostitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 2 / 267 (0.75%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sepsis pasteurella | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tick-borne viral encephalitis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 0 / 267 (0.00%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 3 / 267 (1.12%) | 0 / 260 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Metabolism and nutrition disorders | | | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | 1 / 260 (0.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | 2 / 260 (0.77%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | 0 / 260 (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 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | 0 / 260 (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 |

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

| Non-serious adverse events | Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg |
|---|-------------------|----------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 80 / 260 (30.77%) | 72 / 267 (26.97%) | 77 / 260 (29.62%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 260 (5.00%) | 15 / 267 (5.62%) | 22 / 260 (8.46%) |
| occurrences (all) | 14 | 16 | 28 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 260 (5.00%) | 7 / 267 (2.62%) | 12 / 260 (4.62%) |
| occurrences (all) | 15 | 8 | 13 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 18 / 260 (6.92%) | 16 / 267 (5.99%) | 13 / 260 (5.00%) |
| occurrences (all) | 21 | 22 | 15 |
| Urinary tract infection | | | |
| subjects affected / exposed | 21 / 260 (8.08%) | 19 / 267 (7.12%) | 21 / 260 (8.08%) |
| occurrences (all) | 32 | 21 | 24 |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 30 / 260 (11.54%) | 24 / 267 (8.99%) | 24 / 260 (9.23%) |
| occurrences (all) | 31 | 24 | 25 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 20 December 2017 | Amendment 1: 1. Change to exclusion criterion and guidance on contraceptive methods. 2. Change to exclusion criterion and temporary IMP discontinuation. 3. Change to exclusion criterion to clarify that subjects should not be enrolled in case of any concomitant condition or major systemic disorder that in investigator's opinion could affect their safety during the study. 4. Change to hepatitis serology test at screening. 5. Change to exclusion criterion to clarify that subjects should not be enrolled if currently enrolled in other investigational studies. 6. Change to the exclusion criterion requiring stability of insulin dose. 7. Change to the general guidelines for reporting of AEs. 8. Remove urgent coronary revascularizations from the events subject to the Clinical Endpoint Committees (CECs) review. 9. Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation. 10. Changes to the observation period for safety endpoints. 11. Change to code breaking related to pharmacokinetic (PK) laboratory. 12. Change to the definition of one Event of Special Interest (EOSI), "volume depletion". 13. Change to definition of baseline for estimated glomerular filtration rate (eGFR). 14. Change to instruction for blood pressure measurement. 15. Change to rescue therapy. 16. Change to urine laboratory test. 17. Change in the order of secondary objectives and endpoints for the study. 18. Addition of femoral neck as a region for the bone mineral density (BMD) assessments. 19. Other minor changes for corrections of inconsistency, editorial changes, or administration clarification. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported