



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin Added to Metformin in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-001800-49 |
| Trial protocol | HU SK |
| Global end of trial date | 22 March 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 03 July 2020 |
| First version publication date | 03 July 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC14834 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02926950 |
| WHO universal trial number (UTN) | U1111-1181-6145 |

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 | 22 March 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 March 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of sotagliflozin versus placebo on hemoglobin A1c (HbA1c) reduction at week 26 in subjects with type 2 diabetes (T2D) who have inadequate glycemic control with metformin.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form (ICF).

Background therapy:

Subjects were taking metformin at a stable dosage ≥ 1500 milligrams per day (mg/day) for at least 12 weeks before enrollment.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 11 November 2016 |
| 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 | Slovakia: 29 |
| Country: Number of subjects enrolled | Hungary: 48 |
| Country: Number of subjects enrolled | Canada: 52 |
| Country: Number of subjects enrolled | United States: 389 |
| Worldwide total number of subjects | 518 |
| EEA total number of subjects | 77 |

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) | 339 |
| From 65 to 84 years | 176 |

| | |
|-------------------|---|
| 85 years and over | 3 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 87 investigative sites in Canada, Hungary, Slovakia and the United States from 11 November 2016 to 22 March 2019.

Pre-assignment

Screening details:

Subjects with a diagnosis of type 2 diabetes mellitus were enrolled in 1 of 2 treatment groups, Sotagliflozin 400 mg once daily (qd) + Metformin and Placebo + Metformin. Subjects were randomly assigned to the ratio of 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, Monitor, Data analyst, Carer |

Arms

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

Arm description:

Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 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 2 tablets (identical to the sotagliflozin tablet in appearance), once daily, before the first meal of the day.

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

Dosage and administration details:

Metformin was administered orally as prescribed by the Principal Investigator.

| | |
|------------------|----------------------------------|
| Arm title | Sotagliflozin 400 mg + Metformin |
|------------------|----------------------------------|

Arm description:

Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 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 2 tablets, once daily, before the first meal of the day.

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

Dosage and administration details:

Metformin was administered orally as prescribed by the Principal Investigator.

| Number of subjects in period 1 | Placebo + Metformin | Sotagliflozin 400 mg + Metformin |
|---------------------------------------|---------------------|----------------------------------|
| Started | 259 | 259 |
| Completed | 210 | 211 |
| Not completed | 49 | 48 |
| Adverse event | 4 | 6 |
| At the patient's own request | 21 | 25 |
| Lost to follow-up | 7 | 8 |
| Reason not Specified | 17 | 9 |

Baseline characteristics

Reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Placebo + Metformin |
| Reporting group description: Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks. | |
| Reporting group title | Sotagliflozin 400 mg + Metformin |
| Reporting group description: Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks. | |

| Reporting group values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | Total |
|---|---------------------|----------------------------------|-------|
| Number of subjects | 259 | 259 | 518 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 59.9 ± 9.4 | 60.0 ± 10.1 | - |
| Gender categorical Units: Subjects | | | |
| Female | 113 | 117 | 230 |
| Male | 146 | 142 | 288 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 2 | 3 |
| Asian | 19 | 6 | 25 |
| Black or African American | 40 | 28 | 68 |
| Native Hawaiian or other Pacific Islander | 1 | 0 | 1 |
| White | 197 | 223 | 420 |
| Unknown | 1 | 0 | 1 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 106 | 117 | 223 |
| Not Hispanic or Latino | 153 | 140 | 293 |
| Not reported | 0 | 2 | 2 |
| Hemoglobin A1c (HbA1c) Units: percentage of HbA1c arithmetic mean standard deviation | 8.19 ± 0.82 | 8.20 ± 0.78 | - |
| Systolic Blood Pressure (SBP) Units: Millimetre of Mercury (mmHg) arithmetic mean | 133.80 | 134.06 | |

| | | | |
|--------------------|-------------|-------------|---|
| standard deviation | ± 13.95 | ± 13.95 | - |
|--------------------|-------------|-------------|---|

End points

End points reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Placebo + Metformin |
| Reporting group description: Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks. | |
| Reporting group title | Sotagliflozin 400 mg + Metformin |
| Reporting group description: Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks. | |

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26

| | |
|---|---|
| End point title | Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 |
| End point description: Intent-to-treat (ITT) population included all randomised subjects. Missing data was imputed using the retrieved dropouts & washout imputation method. An analysis of covariance (ANCOVA) model was used for the analysis. | |
| End point type | Primary |
| End point timeframe: Baseline and Week 26 | |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------------|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: percentage of HbA1c | | | | |
| least squares mean (standard error) | -0.29 (± 0.079) | -0.77 (± 0.077) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Sotagliflozin Vs Placebo |
| Statistical analysis description: The change from baseline to Week 26 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline HbA1c as a covariate. | |
| Comparison groups | Placebo + Metformin v Sotagliflozin 400 mg + Metformin |

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 518 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in Least Square (LS) Means |
| Point estimate | -0.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.64 |
| upper limit | -0.309 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.084 |

Secondary: Change from Baseline in 2-hour Postprandial Glucose (PPG) following a Mixed Meal at Week 26

| | |
|------------------------|---|
| End point title | Change from Baseline in 2-hour Postprandial Glucose (PPG) following a Mixed Meal at Week 26 |
| End point description: | ITT population included all randomised subjects. Missing data are imputed using control-based copy reference multiple imputation method. An ANCOVA model was used for the analysis. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 26 |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------------|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: millimole per litre (mmol/L) | | | | |
| least squares mean (standard error) | -0.930 (± 0.2353) | -2.502 (± 0.2292) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Sotagliflozin 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 (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline 2-hour postprandial glucose as a covariate. |
| Comparison groups | Placebo + Metformin v Sotagliflozin 400 mg + Metformin |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 518 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.572 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.0538 |
| upper limit | -1.0909 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2457 |

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: | ITT population included all randomised subjects. Missing data was imputed using retrieved dropouts and washout imputation method. An ANCOVA model was used for the analysis. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 26 |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------------|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -0.550 (± 0.1864) | -1.310 (± 0.2089) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Sotagliflozin Vs Placebo |
| Statistical analysis description: | The change from baseline to Week 26 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and baseline fasting plasma glucose as a covariate. |
| Comparison groups | Placebo + Metformin v Sotagliflozin 400 mg + Metformin |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 518 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0007 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2006 |
| upper limit | -0.3198 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2247 |

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: | |
| ITT population included all randomised subjects. Missing data was imputed using retrieved dropouts and washout imputation method. An ANCOVA model was used for the analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 26 | |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------------|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: kilogram (kg) | | | | |
| least squares mean (standard error) | -0.69 (± 0.310) | -2.56 (± 0.331) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Sotagliflozin Vs Placebo |
| Statistical analysis description: | |
| The change from baseline to Week 26 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤8.0, >8.0%) at screening, randomisation strata of mean SBP (<130, ≥130 mmHg) at screening, and country as fixed effects, and country as fixed effects, and baseline weight as a covariate. | |
| Comparison groups | Placebo + Metformin v Sotagliflozin 400 mg + Metformin |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 518 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.591 |
| upper limit | -1.144 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.369 |

Secondary: Change from Baseline in SBP at Week 12 in Subjects with Baseline SBP ≥ 130 mmHg

| | |
|--|--|
| End point title | Change from Baseline in SBP at Week 12 in Subjects with Baseline SBP ≥ 130 mmHg |
| End point description: | |
| Analysis was performed on ITT population in subjects with baseline SBP ≥ 130 mmHg. Missing data was imputed using control-based copy reference multiple imputation method. An ANCOVA model was used for the analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 26 | |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------------|----------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 129 | 137 | | |
| Units: millimetre of mercury (mmHg) | | | | |
| least squares mean (standard error) | -6.92 (\pm 1.233) | -10.21 (\pm 1.270) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Sotagliflozin Vs Placebo |
| Statistical analysis description: | |
| The change from baseline to Week 12 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.0 , $>8.0\%$) at screening, and country as fixed effects, and baseline SBP as a covariate. | |
| Comparison groups | Placebo + Metformin v Sotagliflozin 400 mg + Metformin |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0209 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -3.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.07 |
| upper limit | -0.497 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.422 |

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: | ITT population included all randomised subjects. Missing data was imputed using control-based copy reference multiple imputation method. An ANCOVA model was used for the analysis. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 12 |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------------|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: mmHg | | | | |
| least squares mean (standard error) | -1.87 (± 0.949) | -5.41 (± 0.950) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Sotagliflozin Vs Placebo |
| Statistical analysis description: | The change from baseline to Week 12 is analysed using an ANCOVA model with treatment groups, randomisation strata of HbA1c (≤ 8.0 , $>8.0\%$) at screening, randomization strata of mean SBP (<130 , ≥ 130 mmHg) at screening, and country as fixed effects, and baseline SBP as a covariate. |
| Comparison groups | Placebo + Metformin v Sotagliflozin 400 mg + Metformin |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 518 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -3.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.479 |
| upper limit | -1.592 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.992 |

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. | |
| End point type | Secondary |
| End point timeframe: Week 26 | |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 5.4 | 10.8 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Sotagliflozin Vs Placebo |
| Statistical analysis description: Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.0 , $> 8.0\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis. | |
| Comparison groups | Placebo + Metformin v Sotagliflozin 400 mg + Metformin |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 518 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0238 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 5.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 10.06 |

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. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 26 | |

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|-------------------------------|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 15.8 | 29.7 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Sotagliflozin Vs Placebo |
| Statistical analysis description: | |
| Percentage difference between treatment groups using the Cochran-Mantel-Haenszel test stratified by the randomisation strata of HbA1c (≤ 8.0 , $> 8.0\%$) at screening, randomisation strata of mean SBP (< 130 , ≥ 130 mmHg) at screening. Missing data at Week 26 were assigned a status of nonresponder in the analysis. | |
| Comparison groups | Sotagliflozin 400 mg + Metformin v Placebo + Metformin |
| Number of subjects included in analysis | 518 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 13.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.91 |
| upper limit | 20.89 |

Other pre-specified: Percentage of Subjects with Hypoglycemic Events

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Hypoglycemic Events |
|-----------------|---|

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]. Subjects may be reported in more than one category. Safety population was defined as all randomised subjects who had received at least 1 dose of the double-blind investigational medicinal product

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

End point timeframe:

Up to 79 weeks in the treatment period

| End point values | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | | |
|---|---------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 259 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Any hypoglycemia | 11.6 | 6.6 | | |
| Documented symptomatic hypoglycemia | 6.2 | 3.1 | | |
| Severe or documented symptomatic hypoglycemia | 6.2 | 3.1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to last dose of study drug (up to 79 weeks) + 4 weeks

Adverse event reporting additional description:

Safety population was defined as all randomised subjects who had received at least 1 dose of the double-blind investigational medicinal product (IMP). 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 + Metformin |
|-----------------------|---------------------|

Reporting group description:

Following a 2-week run-in period, matching placebo was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.

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

Reporting group description:

Following a 2-week run-in period, sotagliflozin 400 mg was administered as 2 tablets, once daily, before the first meal of the day plus metformin as prescribed by the Principal Investigator for up to 26 weeks in the double-blind Core Treatment Period, and subjects continued the same treatment in the double-blind Extension Period for up to 53 weeks.

| Serious adverse events | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | |
|---|---------------------|----------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 259 (8.88%) | 19 / 259 (7.34%) | |
| number of deaths (all causes) | 1 | 3 | |
| number of deaths resulting from adverse events | 0 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Biliary neoplasm | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intraductal papillary mucinous neoplasm | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive breast carcinoma | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal oncocytoma | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary gland cancer recurrent | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 259 (0.00%) | 2 / 259 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (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 | | | |
| Cervical polyp | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colpocele | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| 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 | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 2 / 259 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 259 (0.77%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar stroke | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral artery thrombosis | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic cerebral infarction | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial venous sinus thrombosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Neurodermatitis | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Calculus urethral | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cyst | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 259 (0.77%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|-----------------|-----------------|--|
| Abscess limb | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 259 (0.00%) | 2 / 259 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 3 / 259 (1.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 259 (0.39%) | 0 / 259 (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 | Placebo + Metformin | Sotagliflozin 400 mg + Metformin | |
|---|---------------------|----------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 109 / 259 (42.08%) | 85 / 259 (32.82%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 13 / 259 (5.02%) | 3 / 259 (1.16%) | |
| occurrences (all) | 13 | 3 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 15 / 259 (5.79%) | 6 / 259 (2.32%) | |
| occurrences (all) | 17 | 7 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 259 (4.25%) | 22 / 259 (8.49%) | |
| occurrences (all) | 12 | 25 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 19 / 259 (7.34%) | 8 / 259 (3.09%) | |
| occurrences (all) | 21 | 9 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 17 / 259 (6.56%) | 5 / 259 (1.93%) | |
| occurrences (all) | 20 | 6 | |
| Nasopharyngitis | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 17 / 259 (6.56%) 20 | 14 / 259 (5.41%) 20 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 20 / 259 (7.72%) 23 | 20 / 259 (7.72%) 22 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 15 / 259 (5.79%) 18 | 16 / 259 (6.18%) 22 | |
| Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all) | 19 / 259 (7.34%) 19 | 14 / 259 (5.41%) 14 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 April 2017 | Amendment 1: 1. Addition of SBP endpoints at Week 26 and Week 79, addition of HbA1c, fasting plasma glucose and body weight endpoints at Week 79. 2. Addition of adverse event leading to an amputation as a new event of special interest. 3. Drug-induced liver injury removed as an event of special interest. 4. Addition of urine cultures in the event of abnormal urinalysis findings. 5. Addition of a Steering Committee to the study. 6. Addition of exclusion criteria at randomisation. |
| 19 December 2017 | Amendment 2: 1. Change to guidance on contraceptive methods. 2. Change to temporary IMP discontinuation. 3. Change to the general guidelines for reporting of adverse events (AEs). 4. Remove urgent coronary revascularizations from the events subject to the Clinical Endpoint Committees (CECs) review. 5. Addition of a new section to describe the independent safety assessments for drug-induced liver injuries (DILI) and amputation. 6. Changes to the observation period for safety endpoints. 7. Change to code breaking related to pharmacokinetic (PK) laboratory. 8. Change to the definition of one Event of Special Interest (EOSI), "volume depletion". 9. Change to definition of baseline for estimated glomerular filtration rate (eGFR). 10. Change to urine laboratory test. 11. Change in the order of secondary objectives and endpoints for the study. 11. 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