



Clinical trial results:

Efficacy and safety of semaglutide versus canagliflozin as add-on to metformin in subjects with type 2 diabetes

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2016-000989-35 |
| Trial protocol | SE IE GB |
| Global end of trial date | 16 November 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 03 December 2019 |
| First version publication date | 03 December 2019 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN9535-4270 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03136484 |
| WHO universal trial number (UTN) | U1111-1180-3651 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novo Nordisk A/S |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880 |
| Public contact | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com |
| Scientific contact | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.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 | 05 June 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of once-weekly dosing of semaglutide subcutaneous (s.c.) 1.0 milligrams (mg) versus once-daily dosing of oral canagliflozin 300 mg on glycaemic control in subjects with type 2 diabetes (T2D) on a background treatment of metformin.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice, including archiving of essential documents, (1996) and FDA 21 CFR 312.120.

Background therapy:

Subjects were to be on a stable treatment for at least 90 days prior to screening with metformin (≥ 1500 mg or maximum tolerated dose) and the medication was to be maintained at the stable, pre-trial dose and frequency during the whole treatment period unless rescue medication was needed.

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 23 January 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Argentina: 74 |
| Country: Number of subjects enrolled | Brazil: 42 |
| Country: Number of subjects enrolled | Canada: 50 |
| Country: Number of subjects enrolled | United Kingdom: 91 |
| Country: Number of subjects enrolled | India: 50 |
| Country: Number of subjects enrolled | Ireland: 29 |
| Country: Number of subjects enrolled | Lebanon: 29 |
| Country: Number of subjects enrolled | Mexico: 56 |
| Country: Number of subjects enrolled | Malaysia: 33 |
| Country: Number of subjects enrolled | Sweden: 34 |
| Country: Number of subjects enrolled | United States: 300 |
| Worldwide total number of subjects | 788 |
| EEA total number of subjects | 154 |

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) | 595 |
| From 65 to 84 years | 193 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 115 sites in 11 countries as follows: Argentina (5), Brazil (2), Canada (8), India (10), Ireland (4), Lebanon (5), Malaysia (5), Mexico (2), Sweden (5), United Kingdom (11) and United States (58).

Pre-assignment

Screening details:

Study design: Body composition (sub-study) was measured using dual x-ray absorptiometry (DXA) scans in a planned subset of randomised subjects.

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 |

Blinding implementation details:

For semaglutide and canagliflozin, the active trial product and the corresponding placebo solutions or tablets were visually identical. The clinical study group and the investigator remained blinded throughout the trial. The blinding was maintained until the database had been released for statistical analysis after database lock (DBL).

Arms

| | |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Semaglutide + canagliflozin placebo |

Arm description:

Subjects received subcutaneous (s.c.) injection of semaglutide once-weekly for 52 weeks. Subjects also received placebo matched to canagliflozin tablet once-daily for 52 weeks.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Canagliflozin placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to canagliflozin tablet once-daily for 52 weeks. Canagliflozin placebo tablets were to be taken orally once daily, swallowed whole, preferably before the first meal of the day.

| | |
|--|------------------------|
| Investigational medicinal product name | Semaglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received s.c. injection of semaglutide once-weekly for 52 weeks: 0.25 mg during weeks 0-4 followed by 0.5 mg during weeks 5-8 and then 1.0 mg during weeks 9-52. Semaglutide 1.5 mL prefilled PDS290 pen-injectors were to be administered s.c. in the thigh, abdomen or upper arm, once-weekly on the same day of the week and at any time of the day irrespective of meals.

| | |
|------------------|-------------------------------------|
| Arm title | Canagliflozin + semaglutide placebo |
|------------------|-------------------------------------|

Arm description:

Subjects received canagliflozin tablet once-daily orally for 52 weeks. Subjects also received placebo matched to semaglutide s.c. injection once-weekly for 52 weeks.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--------------------|
| Investigational medicinal product name | Canagliflozin |
| Investigational medicinal product code | |
| Other name | Invokana 100 mg |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received canagliflozin tablet once-daily orally for 52 weeks: 100 mg tablet during weeks 0-8 followed by 300 mg tablet during weeks 9-52. Canagliflozin tablets were to be taken orally once daily, swallowed whole, preferably before the first meal of the day.

| | |
|--|------------------------|
| Investigational medicinal product name | Semaglutide placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received placebo matched to semaglutide s.c. injection once-weekly for 52 weeks. Semaglutide placebo in 1.5 mL prefilled PDS290 pen-injectors were to be administered s.c. in the thigh, abdomen or upper arm, once-weekly on the same day of the week and at any time of the day irrespective of meals.

| Number of subjects in period 1 | Semaglutide + canagliflozin placebo | Canagliflozin + semaglutide placebo |
|---------------------------------------|--|--|
| Started | 394 | 394 |
| Completed | 367 | 372 |
| Not completed | 27 | 22 |
| Death | 1 | - |
| Withdrawal by Subject | 19 | 14 |
| Lost to follow-up | 7 | 8 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Semaglutide + canagliflozin placebo |
| Reporting group description: Subjects received subcutaneous (s.c.) injection of semaglutide once-weekly for 52 weeks. Subjects also received placebo matched to canagliflozin tablet once-daily for 52 weeks. | |
| Reporting group title | Canagliflozin + semaglutide placebo |
| Reporting group description: Subjects received canagliflozin tablet once-daily orally for 52 weeks. Subjects also received placebo matched to semaglutide s.c. injection once-weekly for 52 weeks. | |

| Reporting group values | Semaglutide + canagliflozin placebo | Canagliflozin + semaglutide placebo | Total |
|---|--|--|-------|
| Number of subjects | 394 | 394 | 788 |
| Age Categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 312 | 283 | 595 |
| From 65-84 years | 82 | 111 | 193 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 55.7 | 57.5 | |
| standard deviation | ± 11.1 | ± 10.7 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 171 | 193 | 364 |
| Male | 223 | 201 | 424 |
| HbA1c Units: Percentage (%) of HbA1c | | | |
| arithmetic mean | 8.3 | 8.2 | |
| standard deviation | ± 1.0 | ± 1.0 | - |

End points

End points reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Semaglutide + canagliflozin placebo |
| Reporting group description: Subjects received subcutaneous (s.c.) injection of semaglutide once-weekly for 52 weeks. Subjects also received placebo matched to canagliflozin tablet once-daily for 52 weeks. | |
| Reporting group title | Canagliflozin + semaglutide placebo |
| Reporting group description: Subjects received canagliflozin tablet once-daily orally for 52 weeks. Subjects also received placebo matched to semaglutide s.c. injection once-weekly for 52 weeks. | |

Primary: Change in HbA1c

| | |
|---|-----------------|
| End point title | Change in HbA1c |
| End point description: Change from baseline (week 0) to week 52 in glycosylated haemoglobin (HbA1c) was evaluated for full analysis set which comprised of all randomised subjects. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose to either the day of last dose plus 7 days or first initiation of rescue medication, whichever came first; and 'In-trial' observation period which started at the date of randomisation and include the period after initiation of rescue medication and/or premature trial product discontinuation, if any and ended at the last contact, withdrawal of consent or death, whichever came first. 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group. | |
| End point type | Primary |
| End point timeframe: From baseline to week 52 | |

| End point values | Semaglutide + canagliflozin placebo | Canagliflozin + semaglutide placebo | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 394 | 394 | | |
| Units: Percentage (%) of HbA1c | | | | |
| arithmetic mean (standard deviation) | | | | |
| On-treatment without rescue medication (n=293,313) | -1.7 (± 1.1) | -1.0 (± 1.0) | | |
| In-trial (n=361,362) | -1.5 (± 1.3) | -1.0 (± 1.1) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Primary non-inferiority analysis |
| Statistical analysis description: The responses were analysed using an analysis of covariance (ANCOVA) with treatment, region and stratification factor as fixed factors and baseline value as covariate. Before analysis, missing data were multiple imputed using observed data from participants within the same group defined by randomised treatment, using a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates. | |
| Comparison groups | Canagliflozin + semaglutide placebo v Semaglutide + |

| | |
|---|--------------------------------|
| | canagliflozin placebo |
| Number of subjects included in analysis | 788 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| P-value | < 0.0001 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Treatment difference |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | -0.33 |

Notes:

[1] - "Number of subjects in this analysis" is being erroneously shown as '788'. Actual number of subjects contributed to the analysis and with measurement at week 52 = 606.

[2] - The non-inferiority p-value was calculated as two times the one-sided p-value from a t-distributed test statistic comparing the treatment contrast with 0.3 rather than zero as in a superiority test.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Primary superiority analysis |
|-----------------------------------|------------------------------|

Statistical analysis description:

The responses were analysed using an ANCOVA with treatment, region and stratification factor as fixed factors and baseline value as covariate. Before analysis, missing data were multiple imputed using observed data from participants within the same group defined by randomised treatment, using a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates.

| | |
|---|---|
| Comparison groups | Semaglutide + canagliflozin placebo v Canagliflozin + semaglutide placebo |
| Number of subjects included in analysis | 788 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Treatment difference |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | -0.33 |

Notes:

[3] - "Number of subjects in this analysis" is being erroneously shown as '788'. Actual number of subjects contributed to the analysis and with measurement at week 52 = 606.

Secondary: Change in Fasting Plasma Glucose (FPG)

| | |
|-----------------|--|
| End point title | Change in Fasting Plasma Glucose (FPG) |
|-----------------|--|

End point description:

Change from baseline (week 0) to week 52 in FPG was evaluated for full analysis set which comprised of all randomised subjects. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose to either the day of last dose plus 7 days or first initiation of rescue medication, whichever came first. "Number of subjects analyzed"= subjects with available data.

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

End point timeframe:

From baseline to week 52

| End point values | Semaglutide + canagliflozin placebo | Canagliflozin + semaglutide placebo | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 293 | 305 | | |
| Units: Millimoles per liter (mmol/L) | | | | |
| arithmetic mean (standard deviation) | -2.54 (± 2.77) | -2.00 (± 2.53) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic and diastolic blood pressure

| | |
|---|---|
| End point title | Change in systolic and diastolic blood pressure |
| End point description: | |
| Change from baseline (week 0) to week 52 in systolic blood pressure and diastolic blood pressure was evaluated for full analysis set which comprised of all randomised subjects. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose to either the day of last dose plus 7 days or first initiation of rescue medication, whichever came first. 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to week 52 | |

| End point values | Semaglutide + canagliflozin placebo | Canagliflozin + semaglutide placebo | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 298 | 313 | | |
| Units: Millimeters of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic blood pressure (n=298,313) | -3.7 (± 14.0) | -5.8 (± 13.5) | | |
| Diastolic blood pressure (n=298,313) | -1.2 (± 9.8) | -2.9 (± 9.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Diabetes Treatment Satisfaction Questionnaire (DTSQ): Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately

| | |
|-----------------|---|
| End point title | Change in Diabetes Treatment Satisfaction Questionnaire (DTSQ): Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately |
|-----------------|---|

End point description:

Change from baseline (week 0) in DTSQ was evaluated for full analysis set comprised of all randomised subjects. The DTSQs items are scored on a 7-point graded response scale ranging from 6 to 0. Higher scores indicate higher levels of treatment satisfaction for DTSQs items 1, 4 -8. For items 2 and 3 a higher score indicate higher patient perceived experience of high blood sugars and low blood sugars, respectively. Thus, lower scores indicate a perception of blood glucose levels being "none of the time" unacceptably high (item 2) or low (item 3). The domain score of total treatment satisfaction (total treatment satisfaction score) was computed by adding the six items scores 1, 4-8. The score ranges 0-36. A higher treatment satisfaction score indicates a higher level of treatment satisfaction. Results are based on the 'on-treatment without rescue medication' observation period. 'n' is the number of subjects (subjects with available data) analysed for the respective reporting group.

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

End point timeframe:

From baseline to week 52

| End point values | Semaglutide + canagliflozin placebo | Canagliflozin + semaglutide placebo | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 263 | 280 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1)Satisfaction with treatment (n=263,280) | 1.4 (± 1.6) | 1.0 (± 1.6) | | |
| 2)Experienced high blood sugar (n=263,280) | -2.0 (± 2.2) | -1.8 (± 2.2) | | |
| 3)Experienced low blood sugar (n=263,280) | 0.1 (± 1.9) | 0.1 (± 1.6) | | |
| 4)Convenience of treatment (n=263,280) | 0.8 (± 1.8) | 0.7 (± 1.8) | | |
| 5)Flexibility of current treatment (n=263,280) | 0.8 (± 1.7) | 0.7 (± 1.7) | | |
| 6)Satisfied understanding diabetes (n=263,280) | 0.8 (± 1.5) | 0.6 (± 1.3) | | |
| 7)Recommending treatment to others (n=263,280) | 0.9 (± 1.5) | 0.9 (± 1.5) | | |
| 8)Satisfied to continue treatment (n=263,280) | 1.1 (± 1.8) | 0.8 (± 1.8) | | |
| Total treatment satisfaction score (n=263,280) | 5.8 (± 7.0) | 4.8 (± 7.2) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of trial product (week 0) to end of treatment (week 52) + 42 days

Adverse event reporting additional description:

Evaluation of safety was based on SAS which comprised of all randomised participants who received at least one dose of trial product.

'Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from adverse events'.

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

Dictionary used

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

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

Reporting groups

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|-----------------------|-------------------------------------|
| Reporting group title | Canagliflozin + semaglutide placebo |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received canagliflozin tablet once-daily orally for 52 weeks. Subjects also received placebo matched to semaglutide s.c. injection once-weekly for 52 weeks.

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Semaglutide + canagliflozin placebo |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received s.c. injection of semaglutide once-weekly for 52 weeks. Subjects also received placebo matched to canagliflozin tablet once-daily for 52 weeks.

| Serious adverse events | Canagliflozin + semaglutide placebo | Semaglutide + canagliflozin placebo | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 394 (5.33%) | 18 / 392 (4.59%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| 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 pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (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 | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Bartholin's cyst | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatism | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Airway complication of anaesthesia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Patella fracture | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematuria | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prescribed overdose | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | | |
|--------------------------------------|---|-----------------|-----------------|--|
| Aphasia | subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal ganglia haemorrhage | subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | | |
| Splenomegaly | subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | | |
| Vertigo | subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | | |
| Cataract | subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal infarction | | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 394 (0.76%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis gangrenous | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (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 | 0 / 394 (0.00%) | 3 / 392 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval abscess | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (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 | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Canagliflozin + semaglutide placebo | Semaglutide + canagliflozin placebo | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 120 / 394 (30.46%) | 185 / 392 (47.19%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 27 / 394 (6.85%) | 26 / 392 (6.63%) | |
| occurrences (all) | 47 | 48 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 23 / 394 (5.84%) | 20 / 392 (5.10%) | |
| occurrences (all) | 23 | 20 | |
| Diarrhoea | | | |
| subjects affected / exposed | 37 / 394 (9.39%) | 59 / 392 (15.05%) | |
| occurrences (all) | 58 | 94 | |
| Dyspepsia | | | |
| subjects affected / exposed | 8 / 394 (2.03%) | 22 / 392 (5.61%) | |
| occurrences (all) | 8 | 23 | |
| Nausea | | | |
| subjects affected / exposed | 26 / 394 (6.60%) | 89 / 392 (22.70%) | |
| occurrences (all) | 30 | 127 | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 394 (2.28%) | 50 / 392 (12.76%) | |
| occurrences (all) | 9 | 77 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 21 / 394 (5.33%) | 11 / 392 (2.81%) | |
| occurrences (all) | 21 | 11 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 26 / 394 (6.60%) | 23 / 392 (5.87%) | |
| occurrences (all) | 34 | 25 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 6 / 394 (1.52%) | 26 / 392 (6.63%) | |
| occurrences (all) | 6 | 26 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 16 December 2016 | This protocol amendment introduced: 1. Risk-mitigation strategy for the risk of lower limb amputations potentially associated with canagliflozin. This strategy included additional exclusion and premature discontinuation criteria, physical examination of legs and feet at every site visits and description of this potential risk. 2. Updated identified risks for semaglutide. 3. Other minor corrections and clarifications. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31540867>