

**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
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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
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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
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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
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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)
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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
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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			
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Canagliflozin + semaglutide placebo
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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
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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			
Splénomegaly			
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>