Clinical trial results:
Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin alone or basal insulin in combination with metformin in subjects with type 2 diabetes

Summary

EudraCT number	2013-004502-26
Trial protocol	DE SK
Global end of trial date	21 November 2015

Results information

Result version number	v1 (current)
This version publication date	03 December 2016
First version publication date	03 December 2016

Trial information

Trial identification

Sponsor protocol code	NN9535-3627

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02305381
WHO universal trial number (UTN)	U1111-1149-3738
Other trial identifiers	Japanese trial registration: JapicCTI-142729

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR 1452), Novo Nordisk A/S, 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	29 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2015
Global end of trial reached?	Yes
Global end of trial date	21 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate superiority of once-weekly dosing of two dose levels (0.5 mg and 1.0 mg) of semaglutide versus placebo on glycaemic control in subjects with type 2 diabetes (T2D) on basal insulin.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, EN ISO 14155 Part 1 and 2 and FDA 21 CFR 312.120.

Background therapy:

Subjects were to continue pre-trial background medication throughout the entire trial. Basal insulin with or without metformin were considered background medication.

Evidence for comparator:

Not applicble

Actual start date of recruitment	01 December 2014
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	Germany: 70
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Serbia: 45
Country: Number of subjects enrolled	Slovakia: 40
Country: Number of subjects enrolled	United States: 180
Worldwide total number of subjects	396
EEA total number of subjects	110

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)	281
From 65 to 84 years	114
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 90 sites in 5 countries, as follows: Germany: 10 sites; Japan: 6 sites; Serbia: 4 sites; Slovakia: 5 sites; United States: 65.

Pre-assignment

Screening details:

Not applicable

Period 1

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

Blinding implementation details:

Semaglutide and placebo were supplied in similar 1.5 mL pre-filled PDS290 pen-injector and were by all means visually identical and were packed and labelled to fulfil the requirements for double-blind procedures. Furthermore, equal volumes of semaglutide and placebo were administered during treatment ensuring blinding within dose-level.

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 0.5 mg

Arm description:

Subjects received semaglutide 0.25 mg subcutaneous (sc) injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30.

Arm type	Experimental
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:

Semaglutide injection was administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections were to be administered on the same day of the week during the trial.

Arm title	Semaglutide 1.0 mg

Arm description:

Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30.

Arm type	Experimental
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:

Semaglutide injection was administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections were to be administered on the same day of the week during the trial.

Arm title	Placebo

Arm description:

Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo injection was administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections were to be administered on the same day of the week during the trial.

Number of subjects in period 1	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo
Started	132	131	133
Premature discontinuation of treatment	14 [1]	16 [2]	13 [3]
Completed	127	127	126
Not completed	5	4	7
Not completed	5	4	7

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 0.5 mg
Reporting group description:	
Subjects received semaglutide 0.25 mg subcutaneous (sc) injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30.	
Reporting group title	Semaglutide 1.0 mg
Reporting group description:	
Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 weeks.	

Reporting group values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo
Number of subjects	132	131	133
Age Categorical			
Units: Subjects			
Adults (18-64 years)	93	102	86
From 65-84 years	39	29	46
85 years and over	0	0	1
Age Continuous			
Units: years			
arithmetic mean	59.1	58.5	58.8
standard deviation	± 10.3	± 9	± 10.9
Gender Categorical			
Units: Subjects			
Female	58	54	62
Male	74	77	71
Glycosylated haemoglobin			
Units: percentage of glycosylated haemoglobin			
arithmetic mean	8.36	8.31	8.42
standard deviation	± 0.83	± 0.82	± 0.88
Body weight			
Units: kg			
arithmetic mean	92.74	92.49	89.88
standard deviation	± 19.57	± 22.23	± 21.06
Fasting plasma glucose			
Units: mg/dL			
arithmetic mean	161	152.5	154.1
standard deviation	± 62.38	± 50.91	± 46.66
Insulin Dose			
Number of subjects analysed for this parameter=131, 131 and 133			
Units: international unit			
median	35	36	36
full range (min-max)	15 to 300	14 to 320	12 to 124
Diastolic Blood Pressure			
Units: mm Hg			

arithmetic mean	78.89	78.73	79.35
standard deviation	± 9.72	± 9.98	± 9.71
Systolic Blood Pressure			
Units: mm Hg			
arithmetic mean	134.87	134.4	134.99
standard deviation	± 15	± 16.32	± 16.68
Diabetes Treatment Satisfaction Questionnaire			
The DTSQs questionnaire was used to assess subjects' treatment satisfaction and contained 8 components and evaluates the diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings towards the treatment. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Response options range from 6 (best case) to 0 (worst case). Total scores for treatment satisfaction range from 0-36. Higher scores indicate higher satisfaction.			
Units: scores on a scale			
arithmetic mean	28.86	28.62	27.54
standard deviation	± 6.35	± 6.45	± 6.55

Reporting group values	Total		
Number of subjects	396		
Age Categorical			
Units: Subjects			
Adults (18-64 years)	281		
From 65-84 years	114		
85 years and over	1		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Units: Subjects			
Female	174		
Male	222		
Glycosylated haemoglobin			
Units: percentage of glycosylated haemoglobin			
arithmetic mean			
standard deviation	-		
Body weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Fasting plasma glucose			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Insulin Dose			
Number of subjects analysed for this parameter=131, 131 and 133			
Units: international unit			
median			
full range (min-max)	-		
Diastolic Blood Pressure			
Units: mm Hg			
arithmetic mean			

standard deviation	-		
Systolic Blood Pressure Units: mm Hg arithmetic mean standard deviation	- -		
Diabetes Treatment Satisfaction Questionnaire			
The DTSQs questionnaire was used to assess subjects' treatment satisfaction and contained 8 components and evaluates the diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings towards the treatment. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Response options range from 6 (best case) to 0 (worst case). Total scores for treatment satisfaction range from 0-36. Higher scores indicate higher satisfaction.			
Units: scores on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Semaglutide 0.5 mg
Reporting group description:	
Subjects received semaglutide 0.25 mg subcutaneous (sc) injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30.	
Reporting group title	Semaglutide 1.0 mg
Reporting group description:	
Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 weeks.	

Primary: Change in HbA1c

End point title	Change in HbA1c
End point description:	
Estimated mean change from baseline in HbA1c at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Analysis was performed on full analysis set which included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo.	
End point type	Primary
End point timeframe:	
From baseline to week 30	

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: percentage of glycosylated hemoglobin				
least squares mean (standard error)	-1.45 (± 0.09)	-1.85 (± 0.09)	-0.09 (± 0.09)	

Statistical analyses

Statistical analysis title	Analysis 1: Semaglutide 1.0 mg vs Placebo

Statistical analysis description:

Hierarchical testing was performed as per sequence listed below:Change in HbA1c: semaglutide 1.0 mg vs placebo. Change in HbA1c: semaglutide 0.5 mg vs placebo. Change in body weight: semaglutide 1.0 mg vs placebo. Change in body weight: semaglutide 0.5 mg vs placebo. Analysis was performed using MMRM with treatment, country and stratification variable (HbA1c at screening [≤8.0% or >8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate

Comparison groups	Semaglutide 1.0 mg v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	-1.5

Notes:

[1] - Superiority for change in HbA1c was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0%

Statistical analysis title	Analysis 2: Semaglutide 1.0 mg vs Placebo

Statistical analysis description:

Hierarchical testing was performed as per sequence listed below:Change in HbA1c: semaglutide 1.0 mg vs placebo. Change in HbA1c: semaglutide 0.5 mg vs placebo. Change in body weight: semaglutide 1.0 mg vs placebo. Change in body weight: semaglutide 0.5 mg vs placebo. Analysis was performed using MMRM with treatment, country and stratification variable (HbA1c at screening [≤8.0% or >8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate

Comparison groups	Semaglutide 0.5 mg v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	-1.1

Notes:

[2] - Superiority for change in HbA1c was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0%.

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Estimated mean change from baseline in HbA1c at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Analysis was performed on full analysis set.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: kg				
least squares mean (standard error)	-3.67 (± 0.36)	-6.42 (± 0.36)	-1.36 (± 0.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

End point title	Change in fasting plasma glucose (FPG)

End point description:

Estimated mean change from baseline in FPG at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Estimated mean change from baseline in FPG at week 30. Analysis was performed on full analysis set.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: mg/dL				
least squares mean (standard error)	-29.14 (± 3.74)	-42.38 (± 3.76)	-8.51 (± 4.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in insulin dose

End point title	Change in insulin dose

End point description:

Estimated mean change from baseline in insulin dose at week 30 was measured in terms of ratio to baseline. Responses at week 30 are analysed using an Analysis of covariance model with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of

metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using last observation carried forward. Analysis was performed on full analysis set.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: ratio				
least squares mean (standard error)	0.9 (± 0.01)	0.85 (± 0.01)	0.96 (± 0.01)	

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:

Estimated mean change from baseline in systolic and diastolic blood pressure at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Analysis was performed on full analysis set.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: mm Hg				
least squares mean (standard error)				
Diastolic blood pressure	-1.84 (± 0.73)	-1.5 (± 0.74)	-2.17 (± 0.79)	
Systolic blood pressure	-4.29 (± 1.26)	-7.27 (± 1.27)	-0.99 (± 1.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in patient reported outcomes, Diabetes Treatment Satisfaction Questionnaire (DTSQ)

End point title	Change in patient reported outcomes, Diabetes Treatment Satisfaction Questionnaire (DTSQ)

End point description:

The DTSQs questionnaire was used to assess subjects' treatment satisfaction and contained 8 components and evaluates the diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings towards the treatment. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Response options range from 6 (best case) to 0 (worst case). Total scores for treatment satisfaction range from 0-36. Higher scores indicate higher satisfaction. The post-baseline responses are analysed using an ANCOVA model with treatment, country and stratification variables (HbA1c level at screening [<= 8.0% or > 8.0%] and use of metformin [yes or no]) as fixed factors and baseline value as covariate. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using last observation carried forward. Analysis was performed on full analysis set.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: Scores on a scale				
least squares mean (standard error)	2.73 (± 0.46)	3.47 (± 0.46)	1.25 (± 0.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c below 7.0% (53 mmol/mol) American Diabetes Association (ADA) target

End point title	HbA1c below 7.0% (53 mmol/mol) American Diabetes Association (ADA) target

End point description:

Percentage of subjects with HbA1C below 7.0% after 30 weeks treatment. Missing data imputed from a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Analysis was performed on full analysis set.

End point type	Secondary

End point timeframe:

After 30 weeks treatment

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: percentage of subjects				
number (not applicable)	60.6	78.6	10.5	

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c below or equal to 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target

End point title	HbA1c below or equal to 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target

End point description:

Percentage of subjects with HbA1C below 7.0% after 30 weeks treatment. Missing data imputed from a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Analysis was performed on full analysis set.

End point type	Secondary

End point timeframe:

After 30 weeks of treatment

End point values	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	131	133	
Units: percentage of participants				
number (not applicable)	40.9	61.1	4.5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of trial product until the end of the post-treatment follow-up period.The follow-up visit was scheduled to take place 5 weeks after the date of last dose of trial product with a visit window of +7 days (maximum 36 weeks).

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) was defined as an AE that had onset date (or increased in severity) during the 'on-treatment' observation period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Semaglutide 0.5 mg

Reporting group description:

Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30.

Reporting group title	Semaglutide 1.0 mg

Reporting group description:

Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 weeks.

Serious adverse events	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 132 (6.06%)	12 / 131 (9.16%)	9 / 133 (6.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Femoral artery occlusion			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Carotid endarterectomy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary arterial stent insertion			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery bypass			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery angioplasty			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stent insertion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 131 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 132 (0.00%)	0 / 131 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 131 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 132 (39.39%)	54 / 131 (41.22%)	34 / 133 (25.56%)
Investigations			
Lipase increased			
subjects affected / exposed	12 / 132 (9.09%)	7 / 131 (5.34%)	4 / 133 (3.01%)
occurrences (all)	15	7	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 132 (4.55%)	9 / 131 (6.87%)	2 / 133 (1.50%)
occurrences (all)	6	9	2
Nausea			

subjects affected / exposed	15 / 132 (11.36%)	22 / 131 (16.79%)	6 / 133 (4.51%)
occurrences (all)	21	23	6
Vomiting			
subjects affected / exposed	8 / 132 (6.06%)	15 / 131 (11.45%)	4 / 133 (3.01%)
occurrences (all)	9	17	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 132 (8.33%)	6 / 131 (4.58%)	14 / 133 (10.53%)
occurrences (all)	14	6	16
Upper respiratory tract infection			
subjects affected / exposed	8 / 132 (6.06%)	1 / 131 (0.76%)	4 / 133 (3.01%)
occurrences (all)	10	1	4
Urinary tract infection			
subjects affected / exposed	2 / 132 (1.52%)	4 / 131 (3.05%)	8 / 133 (6.02%)
occurrences (all)	3	5	11
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 132 (3.79%)	7 / 131 (5.34%)	1 / 133 (0.75%)
occurrences (all)	5	7	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2015	Change and clarify the wording of "Rescue criteria".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported