Clinical trial results:
Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity who have reached target dose during run-in period

Summary

EudraCT number	2017-003473-34
Trial protocol	SE NL PT DK ES
Global end of trial date	20 March 2020

Results information

Result version number	v1 (current)
This version publication date	19 March 2021
First version publication date	19 March 2021

Trial information

Trial identification

Sponsor protocol code	NN9536-4376

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03548987
WHO universal trial number (UTN)	U1111-1201-0898

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	16 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2020
Global end of trial reached?	Yes
Global end of trial date	20 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity who have reached target dose of semaglutide during the run-in period, on body weight.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) ICH Good Clinical Practice (2016) and FDA 21 CFR 312.120.

Background therapy: -

Evidence for comparator:

Not applicable.

Actual start date of recruitment	04 June 2018
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	Switzerland: 69
Country: Number of subjects enrolled	Denmark: 60
Country: Number of subjects enrolled	Spain: 70
Country: Number of subjects enrolled	Israel: 60
Country: Number of subjects enrolled	Netherlands: 42
Country: Number of subjects enrolled	Portugal: 35
Country: Number of subjects enrolled	Sweden: 49
Country: Number of subjects enrolled	Ukraine: 66
Country: Number of subjects enrolled	United States: 381
Country: Number of subjects enrolled	South Africa: 70
Worldwide total number of subjects	902
EEA total number of subjects	256

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	844
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 73 sites in Denmark (2), Israel (6), Netherlands (3), Portugal (6), South Africa (6), Spain (7), Sweden (4), Switzerland (6), Ukraine (5), and United States (28).

Pre-assignment

Screening details:

Subjects started with Semaglutide 0.25 mg dose from week 0 to 20 (run-in period) and the dose was increased every 4th week until 2.4 mg was reached. The run-in completers were randomised in 2:1 ratio either to receive semaglutide 2.4 mg or placebo till 48 weeks. The treatment is an adjunct to reduced-calorie diet and increased physical activity.

Period 1

Period 1 title	Run-in period (week 0 to week 20)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial products Semaglutide B 1.0 mg/mL and Semaglutide B 3.0 mg/mL were packed open labelled during the run-in period (0-20 weeks)

Arms

Arm title	Semaglutide

Arm description:

Subjects were to receive once-weekly subcutaneous (s.c) injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly semaglutide s.c 2.4 mg until week 68.

Arm type	Experimental
Investigational medicinal product name	Semaglutide
Investigational medicinal product code	
Other name	Semaglutide B 1.0 mg/mL PDS290, Semaglutide B 3.0 mg/mL PDS290
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg

Number of subjects in period 1	Semaglutide
Started	902
Completed	803
Not completed	99
Consent withdrawn by subject	11
Adverse event, non-fatal	48
Other	9
Pregnancy	1

Run-in failure	19
Lost to follow-up	8
Safety concern as judged by investigator	2
Protocol deviation	1

Period 2

Period 2 title	Maintenance period (week 20 to week 68)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Semaglutide ((Semaglutide B 3.0 mg/mL PDS290) and placebo were identical in appearance and were packed and labelled to fulfil the requirements for double-blind procedures. The subjects, investigators and Novo Nordisk remained blinded during the randomised (maintenance) period and follow-up period and until after data base lock (DBL).

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 2.4 mg

Arm description:

Subjects were to receive once-weekly subcutaneous (s.c) injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly semaglutide s.c 2.4 mg until week 68.

Arm type	Experimental
Investigational medicinal product name	Semaglutide B 3.0 mg/mL PDS290
Investigational medicinal product code	
Other name	semaglutide
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2.4 mg/week

Arm title	Placebo

Arm description:

Subjects were to receive once-weekly s.c injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly placebo until week 68.

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

Dosage and administration details:

2.4 mg/week

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: To comply with the aim of the withdrawal trial design, the period 2 (week 20 to week 68) was considered as baseline since the subjects who have reached the target dose of semaglutide during period 1 (week 0 to week 20) were randomised at week 20 to receive either semaglutide or placebo.

Number of subjects in period 2[2]	Semaglutide 2.4 mg	Placebo
Started	535	268
Completed	504	237
Not completed	31	31
Consent withdrawn by subject	1	1
Adverse event, non-fatal	13	6
Other	12	23
Pregnancy	2	-
Lost to follow-up	2	1
Protocol deviation	1	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out 902 subjects who were enrolled worldwide, 99 subjects have not completed the run-in period (0-20 weeks). Thus, 803 subjects who have completed run-in were randomised in baseline period (20-68 weeks).

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects were to receive once-weekly subcutaneous (s.c) injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly semaglutide s.c 2.4 mg until week 68.

Reporting group title	Placebo

Reporting group description:

Subjects were to receive once-weekly s.c injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly placebo until week 68.

Reporting group values	Semaglutide 2.4 mg	Placebo	Total
Number of subjects	535	268	803
Age Categorical Units: Subjects			
Adults (18-64 years)	503	252	755
From 65-84 years	32	16	48
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	47	46	
standard deviation	± 12	± 12	-
Gender Categorical Units: Subjects			
Female	429	205	634
Male	106	63	169

End points

End points reporting groups

Reporting group title	Semaglutide

Reporting group description:

Subjects were to receive once-weekly subcutaneous (s.c) injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly semaglutide s.c 2.4 mg until week 68.

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects were to receive once-weekly subcutaneous (s.c) injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly semaglutide s.c 2.4 mg until week 68.

Reporting group title	Placebo

Reporting group description:

Subjects were to receive once-weekly s.c injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20, to receive once weekly placebo until week 68.

Primary: Change in body weight (%)

End point title	Change in body weight (%)

End point description:

Change in body weight from baseline (week 20) to week 68 is presented. The endpoint was evaluated based on the data from both in-trial and on-treatment observation periods. In-trial observation period: the uninterrupted time interval from start of run-in (week 0) to last trial-related subject-site contact (week 75). On-treatment observation period: includes all time intervals in which subjects are considered to be on treatment from the first (week 0) to last trial product administration (week 68) including 2 weeks of follow-up. It excludes any period of temporary treatment interruption. Temporary treatment interruption is defined as more than 2 consecutive missed doses (off-treatment period).

End point type	Primary

End point timeframe:

From randomisation (week 20) to week 68

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	520	250		
Units: Percentage point				
arithmetic mean (standard deviation)				
In-trial observation period	-8.3 (± 8.1)	6.5 (± 7.7)		
On-treatment observation period	-8.8 (± 7.8)	6.1 (± 7.7)		

Statistical analyses

Statistical analysis title	Semaglutide 2.4 mg vs Placebo

Statistical analysis description:

ANCOVA: Week 68 responses were analysed using an analysis of covariance model with randomised treatment as factor and baseline body weight as covariate. RD-MI: Missing observations were multiple (x1000) imputed from retrieved subjects of the same randomised treatment arm.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-14.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	-13.5

Notes:

[1] - Treatment policy estimand

Statistical analysis title	Semaglutide 2.4 mg vs Placebo

Statistical analysis description:

MMRM: All responses prior to first discontinuation of treatment (or initiation of other anti-obesity medication or bariatric surgery) were included in a mixed model for repeated measurements with randomised treatment as factor and baseline body weight as covariate, all nested within visit.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-15.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.52
upper limit	-14.13

Notes:

[2] - Hypothetical estimand

Secondary: Change in waist circumference (cm)

End point title	Change in waist circumference (cm)

End point description:

Change in waist circumference from baseline (week 20) to week 68 is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from start of run-in (week 0) to last trial-related subject-site contact (week 75).

End point type	Secondary

End point timeframe:

From randomisation (week 20) to week 68

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	518	248		
Units: Centimeter (cm)				
arithmetic mean (standard deviation)	-6.9 (± 7.5)	3.2 (± 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic blood pressure (mmHg)

End point title	Change in systolic blood pressure (mmHg)

End point description:

Change in systolic blood pressure from week 20 to week 68 is presented. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: the uninterrupted time interval from start of run-in (week 0) to last trial-related subject-site contact (week 75).

End point type	Secondary

End point timeframe:

From randomisation (week 20) to week 68

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	518	248		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)	0 (± 14)	5 (± 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in physical functioning score (SF-36)

End point title	Change in physical functioning score (SF-36)

End point description:

SF-36 is a 36-item patient-reported survey of patient health that measures the subject's overall health-related quality of life (HRQoL). SF-36v2™ questionnaire measured eight domains of functional health and well-being as well as two component summary scores (physical component summary and mental component summary). The 0-100 scale scores from the SF-36 were converted to norm-based scores to enable a direct interpretation in relation to the distribution of the scores in the 2009 U.S. general population. In the metric of norm-based scores, 50 and 10 corresponds to the mean and standard

deviation respectively. Change from week 20 in the domain scores and component summary scores were evaluated at week 68. A positive change score indicates an improvement since baseline. These endpoints were evaluated based on the data from in-trial observation period which is the uninterrupted time interval from start of run-in (week 0) to last trial-related subject-site contact (week 75).

End point type	Secondary

End point timeframe:

From randomisation (week 20) to week 68

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	245		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Change in physical functioning score (SF-36)	1.0 (± 3.8)	-1.2 (± 4.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

week 0 to week 75

Results are based on the SAS which included all subjects who received at least one dose of semaglutide or placebo.

Adverse event reporting additional description:

All AEs mentioned here are TEAE defined as an event that had onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than the date of last dose + 7 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Semaglutide: Run-in period

Reporting group description:

Subjects were to receive once-weekly s.c injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in run-in period (week 0 to week 20) with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached.

Reporting group title	Semaglutide 2.4: Treatment period

Reporting group description:

Subjects were to receive once-weekly s.c injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20. Thus, out of 803, 535 subjects were continued to receive once weekly semaglutide s.c 2.4 mg until week 68.

Reporting group title	Placebo: treatment period

Reporting group description:

Subjects were to receive once-weekly s.c injection of semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL in 20 week run-in period with dose escalation (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) every fourth week until maintenance dose of 2.4 mg of semaglutide was reached. The subjects with target dose reached were randomised in 2:1 at week 20. Thus, out of 803, 268 subjects were switched to receive once weekly placebo until week 68.

Serious adverse events	Semaglutide: Run-in period	Semaglutide 2.4: Treatment period	Placebo: treatment period
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 902 (2.33%)	41 / 535 (7.66%)	15 / 268 (5.60%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			

subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Endometrial cancer stage II			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Haemangioma			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Invasive breast carcinoma			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Lung cancer metastatic			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant melanoma			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Marginal zone lymphoma			

subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Surgical and medical procedures			
Arthroscopic surgery			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Orthognathic surgery			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Pregnancy, puerperium and perinatal conditions			
Morning sickness			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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			
Death			

subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Product issues			
Lead dislodgement			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropod bite			

subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Corneal abrasion			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Fall			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Incisional hernia			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Lower limb fracture			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Meniscus injury			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Road traffic accident			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			

subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 902 (0.22%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	2 / 268 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Nervous system disorders			
Carotid sinus syndrome			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparaesthesia			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Hemiparesis			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Migraine			
subjects affected / exposed	0 / 902 (0.00%)	2 / 535 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			

subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Quadriplegia			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 902 (0.11%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 902 (0.22%)	1 / 535 (0.19%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diverticular perforation			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Vomiting			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Hepatobiliary disorders			
Biliary cyst			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Cholecystitis			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Cholelithiasis			
subjects affected / exposed	0 / 902 (0.00%)	5 / 535 (0.93%)	2 / 268 (0.75%)
occurrences causally related to treatment / all	0 / 0	5 / 5	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 902 (0.22%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ureterolithiasis			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	3 / 902 (0.33%)	0 / 535 (0.00%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Appendicitis			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Diverticulitis			

subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Gastroenteritis			
subjects affected / exposed	0 / 902 (0.00%)	2 / 535 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Induced abortion infection			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pertussis			
subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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
Tooth abscess			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 902 (0.00%)	0 / 535 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 902 (0.11%)	0 / 535 (0.00%)	0 / 268 (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
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 902 (0.00%)	1 / 535 (0.19%)	0 / 268 (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

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

Non-serious adverse events	Semaglutide: Run-in period	Semaglutide 2.4: Treatment period	Placebo: treatment period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	670 / 902 (74.28%)	295 / 535 (55.14%)	114 / 268 (42.54%)
Nervous system disorders			
Headache			
subjects affected / exposed	96 / 902 (10.64%)	41 / 535 (7.66%)	10 / 268 (3.73%)
occurrences (all)	119	48	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	67 / 902 (7.43%)	26 / 535 (4.86%)	6 / 268 (2.24%)
occurrences (all)	69	29	6
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	50 / 902 (5.54%)	8 / 535 (1.50%)	2 / 268 (0.75%)
occurrences (all)	53	10	2
Abdominal pain			
subjects affected / exposed	67 / 902 (7.43%)	34 / 535 (6.36%)	8 / 268 (2.99%)
occurrences (all)	82	45	9
Abdominal pain upper			
subjects affected / exposed	49 / 902 (5.43%)	20 / 535 (3.74%)	3 / 268 (1.12%)
occurrences (all)	64	22	3
Constipation			
subjects affected / exposed	200 / 902 (22.17%)	62 / 535 (11.59%)	16 / 268 (5.97%)
occurrences (all)	232	75	18
Diarrhoea			
subjects affected / exposed	212 / 902 (23.50%)	77 / 535 (14.39%)	19 / 268 (7.09%)
occurrences (all)	309	114	26
Dyspepsia			

subjects affected / exposed	103 / 902 (11.42%)	9 / 535 (1.68%)	2 / 268 (0.75%)
occurrences (all)	127	9	2
Eructation			
subjects affected / exposed	71 / 902 (7.87%)	14 / 535 (2.62%)	1 / 268 (0.37%)
occurrences (all)	88	15	1
Flatulence			
subjects affected / exposed	50 / 902 (5.54%)	14 / 535 (2.62%)	3 / 268 (1.12%)
occurrences (all)	73	44	4
Gastrooesophageal reflux disease			
subjects affected / exposed	58 / 902 (6.43%)	5 / 535 (0.93%)	1 / 268 (0.37%)
occurrences (all)	60	6	1
Nausea			
subjects affected / exposed	422 / 902 (46.78%)	75 / 535 (14.02%)	13 / 268 (4.85%)
occurrences (all)	629	104	13
Vomiting			
subjects affected / exposed	140 / 902 (15.52%)	54 / 535 (10.09%)	8 / 268 (2.99%)
occurrences (all)	239	87	13
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 902 (2.33%)	25 / 535 (4.67%)	14 / 268 (5.22%)
occurrences (all)	23	28	16
Back pain			
subjects affected / exposed	26 / 902 (2.88%)	28 / 535 (5.23%)	18 / 268 (6.72%)
occurrences (all)	28	32	19
Infections and infestations			
Influenza			
subjects affected / exposed	28 / 902 (3.10%)	39 / 535 (7.29%)	19 / 268 (7.09%)
occurrences (all)	28	45	23
Nasopharyngitis			
subjects affected / exposed	92 / 902 (10.20%)	58 / 535 (10.84%)	39 / 268 (14.55%)
occurrences (all)	102	77	54
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	102 / 902 (11.31%)	7 / 535 (1.31%)	0 / 268 (0.00%)
occurrences (all)	115	7	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2018	This protocol is amended for the following reasons: 1. Removal of criteria for discontinuation of trial treatment for subjects included in the trial in violation of the inclusion and/or exclusion criteria and/or randomisation criteria. Subjects will not be discontinued from trial product if considered safe to continue. However, prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted and deviations from the protocol should be avoided. 2. Classifications of risks have been removed from the protocol and instead a reference to the IB or any updates hereof has been added for further details of the risks associated with semaglutide treatment. 3. Minor clarification of content and correction of minor errors and typos.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported