



Clinical trial results:

Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity

Summary

EudraCT number	2017-003436-36
Trial protocol	GB FI DK BG BE PL
Global end of trial date	19 April 2020

Results information

Result version number	v1
This version publication date	19 February 2022
First version publication date	19 February 2022

Trial information

Trial identification

Sponsor protocol code	NN9536-4373
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03548935
WHO universal trial number (UTN)	U1111-1200-8053
Other trial identifiers	JapicCTI: JapicCTI-183991

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsværd, Denmark, 2880
Public contact	Clinical Reporting Office (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (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	17 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2020
Global end of trial reached?	Yes
Global end of trial date	19 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of semaglutide subcutaneous (s.c.) 2.4 mg once-weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on body weight.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (2016) and Food and Drug Administration 21 Code of Federal Regulations 312.120.

Background therapy:

Not applicable

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?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 65
Country: Number of subjects enrolled	Belgium: 60
Country: Number of subjects enrolled	Bulgaria: 45
Country: Number of subjects enrolled	Canada: 63
Country: Number of subjects enrolled	Germany: 100
Country: Number of subjects enrolled	Denmark: 50
Country: Number of subjects enrolled	Finland: 60
Country: Number of subjects enrolled	France: 55
Country: Number of subjects enrolled	United Kingdom: 218
Country: Number of subjects enrolled	India: 117
Country: Number of subjects enrolled	Japan: 100
Country: Number of subjects enrolled	Mexico: 70
Country: Number of subjects enrolled	Poland: 60
Country: Number of subjects enrolled	Russian Federation: 100
Country: Number of subjects enrolled	Taiwan: 35
Country: Number of subjects enrolled	United States: 763

Worldwide total number of subjects	1961
EEA total number of subjects	430

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)	1805
From 65 to 84 years	155
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 129 sites in 16 countries as follows: Argentina (5), Belgium (5), Bulgaria (5), Canada (7), Denmark (1), Finland (2), France (7), Germany (13), India (13), Japan (5), Mexico (3), Poland (4), Russian Federation (8), Taiwan (1), United Kingdom (10), United States (40).

Pre-assignment

Screening details:

The trial included an initial 16-week dose-escalation period and a 52-week dose maintenance period. Subjects were randomized in 2:1 ratio either to receive semaglutide 2.4 mg or placebo. The treatment is an adjunct to reduced-calorie diet and increased physical activity.

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:

Semaglutide and placebo were identical in appearance and were packed and labelled to fulfil the requirements for double-blind procedures.

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 at a starting dose of 0.25 milligrams (mg) and then followed a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once-weekly for an additional 52 weeks until week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

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

Dosage and administration details:

Once-weekly s.c injection of Semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing Semaglutide 3.0 mg/mL at a starting dose of 0.25 milligrams (mg) and then followed a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once-weekly for an additional 52 weeks until week 68. Injections were administered in the thigh, abdomen or upper arm, and at any time of the day irrespective of meals.

Investigational medicinal product name	Semaglutide 1.0 mg/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

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 at a starting dose of 0.25 milligrams (mg) and then followed a fixed-

dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once-weekly for an additional 52 weeks until week 68. Injections were administered in the thigh, abdomen or upper arm, and at any time of the day irrespective of meals.

Arm title	Placebo
Arm description:	
Subjects were to receive once-weekly s.c injection of placebo matched to Semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing Semaglutide 1.0 mg/mL or 3.0 mg/mL for week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.	
Arm type	Placebo
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:

Once-weekly s.c injection of 0.25 mg Semaglutide placebo was administered using a PDS290 pre-filled pen-injector with a 3 mL cartridge. Dosing was once weekly with dose escalation every fourth week until the maintenance dose was reached. Injections could be administered in the thigh, abdomen or upper arm, and at any time of the day irrespective of meals.

Number of subjects in period 1	Semaglutide 2.4 mg	Placebo
Started	1306	655
Full analysis set (FAS)	1306	655
Safety analysis set (SAS)	1306	655
Completed	1240	609
Not completed	66	46
Adverse event, serious fatal	1	1
Consent withdrawn by subject	26	17
Lost to follow-up	39	28

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 at a starting dose of 0.25 milligrams (mg) and then followed a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once-weekly for an additional 52 weeks until week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Subjects were to receive once-weekly s.c injection of placebo matched to Semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing Semaglutide 1.0 mg/mL or 3.0 mg/mL for week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

Reporting group values	Semaglutide 2.4 mg	Placebo	Total
Number of subjects	1306	655	1961
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	46 ± 13	47 ± 12	-
Gender Categorical Units: Subjects			
Female	955	498	1453
Male	351	157	508

End points

End points 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 at a starting dose of 0.25 milligrams (mg) and then followed a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once-weekly for an additional 52 weeks until week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.	
Reporting group title	Placebo
Reporting group description: Subjects were to receive once-weekly s.c injection of placebo matched to Semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing Semaglutide 1.0 mg/mL or 3.0 mg/mL for week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.	

Primary: Change in body weight (%)

End point title	Change in body weight (%)
End point description: Change in body weight from baseline (week 0) 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 date of randomization (week 0) to date of last contact with trial site (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). Full analysis set (FAS) included all randomised subjects according to the intention-to-treat principle.	
End point type	Primary
End point timeframe: From baseline at week 0 to week 68	

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1212	577		
Units: Percentage point				
arithmetic mean (standard deviation)				
In-trial observation period	-15.6 (± 10.1)	-2.8 (± 6.5)		
On-treatment observation period	-16.9 (± 9.4)	-3.1 (± 6.4)		

Statistical analyses

Statistical analysis title	Semaglutide 2.4 mg versus Placebo
Statistical analysis description: Analysis of data from in-trial period. 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.

All subjects in FAS (1961 subjects) contributed to the analysis.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	1789
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-12.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.37
upper limit	-11.51

Notes:

[1] - Treatment policy estimand

Statistical analysis title	Semaglutide 2.4 mg versus Placebo
-----------------------------------	-----------------------------------

Statistical analysis description:

Analysis of data from on-treatment period. Time-point considered as on-treatment if any dose of trial product has been administered within prior 14 days. 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.

All subjects in FAS (1961) contributed to the analysis.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	1789
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-14.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.29
upper limit	-13.55

Notes:

[2] - Hypothetical estimand

Primary: Subjects who achieve body weight reduction \geq 5% (yes/no)

End point title	Subjects who achieve body weight reduction \geq 5% (yes/no)
-----------------	---

End point description:

Number of subjects who achieved weight loss more than or equal to 5% (yes/no) at week 68 are 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 randomization (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. FAS included all randomised subjects according to the intention-to-treat principle.

End point type	Primary
End point timeframe:	
After 68 weeks from baseline at week 0	

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1212	577		
Units: Subjects				
In-trial observation period: Yes	1047	182		
In-trial observation period: No	165	395		
On-treatment observation period: Yes	978	165		
On-treatment observation period: No	81	334		

Statistical analyses

Statistical analysis title	Semaglutide 2.4 mg versus Placebo
Statistical analysis description:	
Analysis of data from on-treatment period. MMRM was performed on body weight (kg) and individual missing week 68 responses were predicted from the MMRM; each subject was then classified for body weight loss $\geq 5\%$ and analysed using a binary logistic regression (LR) model with randomised treatment as factor and baseline body weight as covariate.	
All subjects in FAS (1961 subjects) contributed to the analysis.	
Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	1789
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	37.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.02
upper limit	48.95

Notes:

[3] - Hypothetical estimand

Statistical analysis title	Semaglutide 2.4 mg versus Placebo
Statistical analysis description:	
Results are based on the data from in-trial observation period. Week 68 responses were analysed using a binary logistic regression 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.	
All subjects in FAS (1961 subjects) contributed to the analysis.	
Comparison groups	Semaglutide 2.4 mg v Placebo

Number of subjects included in analysis	1789
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.88
upper limit	14.19

Notes:

[4] - Treatment policy estimand

Secondary: Subjects who achieve (yes/no) body weight reduction \geq 10%

End point title	Subjects who achieve (yes/no) body weight reduction \geq 10%
End point description:	
Number of subjects who achieved weight loss more than or equal to (\geq) 10% at 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 date of randomization (week 0) to date of last contact with trial site (week 75). FAS included all randomised subjects according to the intention-to-treat principle.	
End point type	Secondary
End point timeframe:	
After 68 weeks from baseline at week 0	

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1212	577		
Units: Subjects				
Yes	838	69		
No	374	508		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve (yes/no) body weight reduction \geq 15%

End point title	Subjects who achieve (yes/no) body weight reduction \geq 15%
End point description:	
Number of subjects who achieved more than or equal to (\geq) 15% weight loss at 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 randomization (week 0) to last trial-related subject-site contact (week 75). FAS included all randomised subjects according to the intention-to-treat principle.	
End point type	Secondary

End point timeframe:

After 68 weeks from baseline at week 0

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1212	577		
Units: Subjects				
Yes	612	28		
No	600	549		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference (cm)

End point title	Change in waist circumference (cm)
End point description: Change in waist circumference from baseline (week 0) 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 randomization (week 0) to date of last contact with trial site (week 75). FAS included all randomised subjects according to the intention-to-treat principle.	
End point type	Secondary
End point timeframe: From baseline at week 0 to week 68	

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1210	575		
Units: Centimeter (cm)				
arithmetic mean (standard deviation)	-14.1 (± 9.6)	-4.4 (± 6.9)		

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 baseline (week 0) 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 randomization (week 0) to date of last contact with trial site	

(week 75). FAS included all randomised subjects according to the intention-to-treat principle.

End point type	Secondary
End point timeframe:	
From baseline at week 0 to week 68	

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1210	574		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)	-7 (± 14)	-1 (± 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:	
<p>Short Form 36 version 2.0 acute (SF-36) is a 36-item patient-reported survey of patient health that measures the participant'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). In the metric of norm-based scores, 50 and 10 corresponds to the mean and standard deviation, respectively, for the 2009 US general population. Change from week 0 in the domain scores and component summary scores were evaluated at week 68. A positive change score indicates an improvement since baseline. The endpoint was evaluated based on the data from in-trial observation period which is the uninterrupted time interval from start of randomization (week 0) to last trial-related subject-site contact (week 75). FAS included all randomised subjects according to the intention-to-treat principle.</p>	
End point type	Secondary
End point timeframe:	
From baseline at week 0 to week 68	

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1195	566		
Units: Score on a scale				
arithmetic mean (standard deviation)	2.3 (± 6.6)	0.4 (± 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in physical function domain (5-items) score (IWQoL-Lite for CT)

End point title	Change in physical function domain (5-items) score (IWQoL-Lite for CT)
-----------------	--

End point description:

Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQoL-Lite-CT) is a modified version of an instrument designed to assess weight-related quality of life. It is used to assess the impact of body weight changes on patients' physical and psychosocial functioning in three composite scores (physical function, physical and psychosocial) and a total score. The scores range between 0-100 where higher scores indicate a better quality of life. A positive change score indicates an improvement since baseline. This endpoint was evaluated based on the data from in-trial observation period which is the uninterrupted time interval from start of randomization (week 0) to last trial-related subject-site contact (week 75). FAS included all randomised subjects according to the intention-to-treat principle.

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

End point timeframe:

From baseline at week 0 to week 68

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1193	566		
Units: Score on a scale				
arithmetic mean (standard deviation)	15.0 (± 21.6)	6.0 (± 21.1)		

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 participants 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 randomized 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	Placebo
-----------------------	---------

Reporting group description:

Subjects were to receive once-weekly s.c injection of placebo matched to Semaglutide using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing Semaglutide 1.0 mg/mL or 3.0 mg/mL for week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

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 at a starting dose of 0.25 milligrams (mg) and then followed a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once-weekly for an additional 52 weeks until week 68. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

Serious adverse events	Placebo	Semaglutide 2.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 655 (6.41%)	128 / 1306 (9.80%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Glioblastoma	subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 1	0 / 0
Hairy cell leukaemia	subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Intraductal proliferative breast lesion	subjects affected / exposed	1 / 655 (0.15%)	2 / 1306 (0.15%)
	occurrences causally related to treatment / all	0 / 1	0 / 2
	deaths causally related to treatment / all	0 / 0	0 / 0
Invasive ductal breast carcinoma	subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Leiomyoma	subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian adenoma	subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Papillary thyroid cancer	subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Prostate cancer	subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominoplasty			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone prosthesis insertion			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	1 / 655 (0.15%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric bypass			
subjects affected / exposed	1 / 655 (0.15%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip surgery			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc operation			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal			

conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
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	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent occlusion			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erectile dysfunction			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	2 / 655 (0.31%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	2 / 655 (0.31%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Ankle fracture			
subjects affected / exposed	1 / 655 (0.15%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 655 (0.15%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 655 (0.15%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 655 (0.15%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (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	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 655 (0.31%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
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 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve disorder			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic intracranial hypertension			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	1 / 655 (0.15%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychogenic seizure			

subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haemorrhage			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 655 (0.00%)	3 / 1306 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 655 (0.00%)	3 / 1306 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 655 (0.00%)	4 / 1306 (0.31%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 655 (0.00%)	4 / 1306 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 655 (0.00%)	3 / 1306 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 655 (0.15%)	12 / 1306 (0.92%)	
occurrences causally related to treatment / all	1 / 1	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hidradenitis			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 655 (0.15%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 655 (0.15%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia intercostal			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 655 (0.31%)	3 / 1306 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 655 (0.15%)	5 / 1306 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial colitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 655 (0.00%)	5 / 1306 (0.38%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis astroviral			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (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	2 / 655 (0.31%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 655 (0.00%)	2 / 1306 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxoplasmosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 1306 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 1306 (0.08%)	
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	Placebo	Semaglutide 2.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	447 / 655 (68.24%)	1052 / 1306 (80.55%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	23 / 655 (3.51%)	98 / 1306 (7.50%)	
occurrences (all)	35	129	
Headache			
subjects affected / exposed	80 / 655 (12.21%)	198 / 1306 (15.16%)	
occurrences (all)	104	386	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 655 (4.27%)	104 / 1306 (7.96%)	
occurrences (all)	29	120	
Gastrointestinal disorders			

Abdominal distension subjects affected / exposed occurrences (all)	31 / 655 (4.73%) 42	96 / 1306 (7.35%) 135	
Abdominal pain subjects affected / exposed occurrences (all)	36 / 655 (5.50%) 41	127 / 1306 (9.72%) 172	
Abdominal pain upper subjects affected / exposed occurrences (all)	35 / 655 (5.34%) 37	125 / 1306 (9.57%) 176	
Constipation subjects affected / exposed occurrences (all)	62 / 655 (9.47%) 73	305 / 1306 (23.35%) 389	
Diarrhoea subjects affected / exposed occurrences (all)	104 / 655 (15.88%) 138	411 / 1306 (31.47%) 765	
Dyspepsia subjects affected / exposed occurrences (all)	23 / 655 (3.51%) 30	135 / 1306 (10.34%) 179	
Eructation subjects affected / exposed occurrences (all)	3 / 655 (0.46%) 3	112 / 1306 (8.58%) 139	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	20 / 655 (3.05%) 21	82 / 1306 (6.28%) 92	
Nausea subjects affected / exposed occurrences (all)	114 / 655 (17.40%) 146	576 / 1306 (44.10%) 1067	
Vomiting subjects affected / exposed occurrences (all)	43 / 655 (6.56%) 52	321 / 1306 (24.58%) 632	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	33 / 655 (5.04%) 35	40 / 1306 (3.06%) 45	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	53 / 655 (8.09%)	106 / 1306 (8.12%)	
occurrences (all)	55	120	
Arthralgia			
subjects affected / exposed	43 / 655 (6.56%)	81 / 1306 (6.20%)	
occurrences (all)	47	92	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	30 / 655 (4.58%)	81 / 1306 (6.20%)	
occurrences (all)	38	99	
Influenza			
subjects affected / exposed	63 / 655 (9.62%)	89 / 1306 (6.81%)	
occurrences (all)	79	112	
Nasopharyngitis			
subjects affected / exposed	133 / 655 (20.31%)	281 / 1306 (21.52%)	
occurrences (all)	216	480	
Upper respiratory tract infection			
subjects affected / exposed	80 / 655 (12.21%)	114 / 1306 (8.73%)	
occurrences (all)	116	158	
Sinusitis			
subjects affected / exposed	36 / 655 (5.50%)	70 / 1306 (5.36%)	
occurrences (all)	40	83	
Urinary tract infection			
subjects affected / exposed	28 / 655 (4.27%)	68 / 1306 (5.21%)	
occurrences (all)	33	83	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 655 (3.36%)	124 / 1306 (9.49%)	
occurrences (all)	26	139	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2018	Implementation of genetic biosamples for future analysis for those countries where it will be applicable. 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. Classifications of risks have been removed from the protocol and instead a reference to the investigator's brochure or any updates hereof has been added for further details of the risks associated with semaglutide treatment.
09 May 2019	Trial extension: 52-weeks off-treatment period after end of treatment in the main phase without structured lifestyle intervention in the following countries only: Canada, Germany, the UK and selected sites in the US and Japan.

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/30122305>

<http://www.ncbi.nlm.nih.gov/pubmed/32441473>

<http://www.ncbi.nlm.nih.gov/pubmed/33567185>