Clinical trial results:
Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes

A 52-week, multi-centre, multinational, open-label, activecontrolled, two armed, parallel-group, randomised trial in subjects with type 2 diabetes

Summary

EudraCT number	2017-003219-20
Trial protocol	SK SI EE BG LV PL GR DE CZ LT PT ES HR HU RO
Global end of trial date	22 February 2021

Results information

Result version number	v1 (current)
This version publication date	10 March 2022
First version publication date	10 March 2022

Trial information

Trial identification

Sponsor protocol code	NN9535-4386

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03689374
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2843), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), 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	01 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of once-weekly semaglutide subcutaneously (s.c.) on glycaemic control versus insulin aspart three times daily, both as add on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes (T2D).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and International Council for Harmonisation (ICH) Good Clinical Practice (2016), including archiving of essential documents, EN ISO 14155 and 21 US Code of Federal Regulations (CFR) 312.120.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 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	Bulgaria: 123
Country: Number of subjects enrolled	Bosnia and Herzegovina: 51
Country: Number of subjects enrolled	Czechia: 51
Country: Number of subjects enrolled	Germany: 223
Country: Number of subjects enrolled	Spain: 82
Country: Number of subjects enrolled	Estonia: 34
Country: Number of subjects enrolled	Greece: 129
Country: Number of subjects enrolled	Croatia: 58
Country: Number of subjects enrolled	Hungary: 78
Country: Number of subjects enrolled	India: 346
Country: Number of subjects enrolled	Lithuania: 40
Country: Number of subjects enrolled	Latvia: 73
Country: Number of subjects enrolled	North Macedonia: 45
Country: Number of subjects enrolled	Poland: 271
Country: Number of subjects enrolled	Portugal: 22
Country: Number of subjects enrolled	Romania: 70
Country: Number of subjects enrolled	Serbia: 223
Country: Number of subjects enrolled	Slovakia: 89
Country: Number of subjects enrolled	Slovenia: 35

Country: Number of subjects enrolled	Turkey: 103
Country: Number of subjects enrolled	South Africa: 128
Worldwide total number of subjects	2274
EEA total number of subjects	1378

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)	1422
From 65 to 84 years	849
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Trial conducted at 209 sites (21 countries): Bosnia-Herzegovina (3), Bulgaria (9), Croatia (7), Czech Republic (7), Estonia (5), Germany (25), Greece (14), Hungary (8), India (20), Latvia (7), Lithuania (6), Macedonia (3), Poland (20), Portugal (6), Romania (7), Serbia (14), Slovakia (9), Slovenia (6), South Africa (11), Spain (8) and Turkey (14).

Pre-assignment

Screening details:

This trial consisted of 12-week run-in, 52-week treatment period and subjects were followed up 5 weeks for safety. Subjects were randomised 1:1 to receive treatment with: metformin + insulin glargine (IGlar) U100 + once-weekly semaglutide subcutaneously (s.c). or metformin + insulin glargine U100 + mealtime insulin aspart s.c. three times daily.

Period 1

Period 1 title	Run-in period (12 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All subjects

Arm description:

During run-in period insulin glargine in combination with metformin was to be optimised. All enrolled subjects received metformin orally and IGlar U100 s.c. injection in run-in period. Metformin was optimised in dose range of greater than or equal to (>=) 1500 milligrams (mg) to less than or equal to (<=) 3000 mg. After run-in period, subjects were randomised 1:1 to receive add-on treatment with semaglutide once weekly or insulin aspart three times daily (TID) in treatment period.

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

Dosage and administration details:

subjects received IGlar U100 s.c. injection.

Number of subjects in period 1	All subjects
Started	2274
Completed	1748
Not completed	526
Run-in failure	526

Period 2

Period 2 title	Treatment Period (Week 0 to 52)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide

Arm description:

Subjects received metformin, IGlar U100 and semaglutide up to week 52. Metformin dose was maintained at same level and frequency as optimised in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast self-measured plasma glucose (SMPG) values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of semaglutide at an initiation dose of 0.25 mg once weekly, after 4 weeks dose was increased to 0.5 mg, and 1 mg after at least 4 weeks to further improve glycaemic control, at investigator's discretion. Dose reduction from 1 to 0.5 mg was allowed in case of safety concern/unacceptable intolerability. Subjects were followed up for 5 weeks (week 57) for safety.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	Lantus®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast SMPG values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia.

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

Dosage and administration details:

Subjects self-administered s.c. injection of semaglutide at an initiation dose of 0.25 mg once weekly, after 4 weeks dose was increased to 0.5 mg, and 1 mg after at least 4 weeks to further improve glycaemic control, at investigator's discretion. Dose reduction from 1 to 0.5 mg was allowed in case of safety concern/unacceptable intolerability.

Arm title	Insulin Aspart

Arm description:

Subjects received metformin, IGlar U100 and insulin aspart up to week 52. Metformin dose was maintained at same level and frequency as optimised in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast SMPG values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of insulin aspart at an initiation dose of 4 units three times daily, dose adjustments were considered twice weekly based on pre-prandial and bedtime SMPG from the preceding 3 days and the individualised goal according to investigator's discretion. Subjects were followed up for 5 weeks (week 57) for safety.

Arm type	Active comparator

Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	
Other name	NovoRapid®/NovoLog®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects self-administered s.c. injection of insulin aspart at an initiation dose of 4 units three times daily, dose adjustments were considered twice weekly based on pre-prandial and bedtime SMPG from the preceding 3 days and the individualised goal according to investigator's discretion.

Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	Lantus®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast SMPG values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia.

Notes:

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

Justification: Baseline data was collected only for randomised subject in treatment period.

Number of subjects in period 2[2]	Semaglutide	Insulin Aspart
Started	874	874
Completed	850	831
Not completed	24	43
Consent withdrawn by subject	10	38
Death	11	1
Lost to follow-up	3	4

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: Period 1 was run-in period, baseline data was collected only for subjects randomised in treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide

Reporting group description:

Subjects received metformin, IGlar U100 and semaglutide up to week 52. Metformin dose was maintained at same level and frequency as optimised in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast self-measured plasma glucose (SMPG) values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of semaglutide at an initiation dose of 0.25 mg once weekly, after 4 weeks dose was increased to 0.5 mg, and 1 mg after at least 4 weeks to further improve glycaemic control, at investigator's discretion. Dose reduction from 1 to 0.5 mg was allowed in case of safety concern/unacceptable intolerability. Subjects were followed up for 5 weeks (week 57) for safety.

Reporting group title	Insulin Aspart

Reporting group description:

Subjects received metformin, IGlar U100 and insulin aspart up to week 52. Metformin dose was maintained at same level and frequency as optimised in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast SMPG values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of insulin aspart at an initiation dose of 4 units three times daily, dose adjustments were considered twice weekly based on pre-prandial and bedtime SMPG from the preceding 3 days and the individualised goal according to investigator's discretion. Subjects were followed up for 5 weeks (week 57) for safety.

Reporting group values	Semaglutide	Insulin Aspart	Total
Number of subjects	874	874	1748
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	575	530	1105
From 65-84 years	299	343	642
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	60.8	61.5	
standard deviation	± 9.4	± 9.5	-
Gender Categorical Units: Subjects			
Female	429	425	854
Male	445	449	894

End points

End points reporting groups

Reporting group title	All subjects

Reporting group description:

During run-in period insulin glargine in combination with metformin was to be optimised. All enrolled subjects received metformin orally and IGlar U100 s.c. injection in run-in period. Metformin was optimised in dose range of greater than or equal to (>=) 1500 milligrams (mg) to less than or equal to (<=) 3000 mg. After run-in period, subjects were randomised 1:1 to receive add-on treatment with semaglutide once weekly or insulin aspart three times daily (TID) in treatment period.

Reporting group title	Semaglutide

Reporting group description:

Subjects received metformin, IGlar U100 and semaglutide up to week 52. Metformin dose was maintained at same level and frequency as optimised in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast self-measured plasma glucose (SMPG) values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of semaglutide at an initiation dose of 0.25 mg once weekly, after 4 weeks dose was increased to 0.5 mg, and 1 mg after at least 4 weeks to further improve glycaemic control, at investigator's discretion. Dose reduction from 1 to 0.5 mg was allowed in case of safety concern/unacceptable intolerability. Subjects were followed up for 5 weeks (week 57) for safety.

Reporting group title	Insulin Aspart

Reporting group description:

Subjects received metformin, IGlar U100 and insulin aspart up to week 52. Metformin dose was maintained at same level and frequency as optimised in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast SMPG values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of insulin aspart at an initiation dose of 4 units three times daily, dose adjustments were considered twice weekly based on pre-prandial and bedtime SMPG from the preceding 3 days and the individualised goal according to investigator's discretion. Subjects were followed up for 5 weeks (week 57) for safety.

Primary: Change in HbA1c (%-point)

End point title	Change in HbA1c (%-point)

End point description:

Change from baseline in HbA1c (measured in %) at week 52 is presented. Data is reported for 'on-treatment' observation period: from the date of first dose of trial product (week 0) to the last date on trial product with a visit window of +7 days (week 52). Full analysis set included all randomised subjects. Number of Subjects Anlaysed = subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline (week 0), week 52

End point values	Semaglutide	Insulin Aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	795	783		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-1.5 (± 1.0)	-1.2 (± 1.0)		

Statistical analyses

Statistical analysis title	Semaglutide versus insulin aspart

Statistical analysis description:

The responses were analysed using an ANCOVA with treatment as fixed factor and baseline value as a covariate. Before analysis, missing data were multiple imputed using observed data from subjects within the same group defined by randomised treatment, using a regression model including randomised treatment group and data from baseline and all previous visits as covariates. The prespecified non inferiority margin was 0.3%-point.

Comparison groups	Semaglutide v Insulin Aspart
Number of subjects included in analysis	1578
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [1]
Method	t-distributed test
Parameter estimate	Treatment difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.2

Notes:

[1] - The non-inferiority p-value was calculated as two times the one-sided p-value from a t-distributed test.

Secondary: Time to first event adjudication committee confirmed severe hypoglycaemic episode (American Diabetes Association)

End point title	Time to first event adjudication committee confirmed severe hypoglycaemic episode (American Diabetes Association)

End point description:

Rates per 100 years of exposure time for first EAC confirmed severe hypoglycaemic episodes from randomization (week 0) to week 52 are presented. As per 2013 ADA criteria severe hypoglycaemic episodes were episodes with plasma glucose (PG) less than or equal to (<=) 3.9 millimoles per liter (mmol/L) (70 milligrams per deciliter (mg/dL)). EAC confirmed-severe hypoglycaemia was an episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. Data is reported for 'on-treatment' observation period: from the date of first dose of trial product (week 0) to the last date on trial product with a visit window of +7 days (week 52). Full analysis set included all randomised subjects. Number of Subjects Anlaysed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From randomization (week 0) to week 52

End point values	Semaglutide	Insulin Aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	874	864		
Units: Rate per 100 years of exposure				
number (not applicable)	0.42	0.73		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first event adjudication committee confirmed severe hypoglycaemic episode (American Diabetes Association) requiring hospitalisation, documented medical help, or is life threatening

End point title	Time to first event adjudication committee confirmed severe hypoglycaemic episode (American Diabetes Association) requiring hospitalisation, documented medical help, or is life threatening

End point description:

Rates per 100 years of exposure time for first EAC confirmed severe hypoglycaemic episodes requiring hospitalization, documented medical help, or is life threatening from randomization (week 0) to week 52 are presented. As per 2013 ADA criteria severe hypoglycaemic episodes were episodes with PG <= 3.9 mmol/L (70 mg/dL). EAC confirmed-severe hypoglycaemia was an episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. Data is reported for 'on-treatment' observation period: from the date of first dose of trial product (week 0) to the last date on trial product with a visit window of +7 days (week 52). Full analysis set included all randomised subjects. Number of Subjects Analysed = subjects with available data for this endpoint

End point type	Secondary

End point timeframe:

From randomization (week 0) to week 52

End point values	Semaglutide	Insulin Aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	874	864		
Units: Rate per 100 years of exposure				
number (not applicable)	0.21	0.44		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight (kilograms (kg))

End point title	Change in body weight (kilograms (kg))

End point description:

Change from baseline in body weight (measured in kg) at week 52 is presented. Data is reported for 'on-treatment' observation period: from the date of first dose of trial product (week 0) to the last date on trial product with a visit window of +7 days (week 52). Full analysis set included all randomised subjects. Number of Subjects Analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (week 0), week 52

End point values	Semaglutide	Insulin Aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	801	793		
Units: kilograms				
arithmetic mean (standard deviation)	-4.2 (± 4.6)	2.9 (± 4.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From week 0 to week 52

Adverse event reporting additional description:

All presented adverse events (AEs) are treatment-emergent (i.e., TEAEs). TEAEs were defined as AEs with onset during the 'on-treatment' observation period. Results are based on the safety analysis set (SAS) which included all subjects exposed to at least one dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Insulin Aspart

Reporting group description:

Subjects received metformin, IGlar U100 and insulin aspart for 52 weeks in treatment period. Metformin dose was maintained at same level and frequency as optimized in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast SMPG values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of insulin aspart at an initiation dose of 4 units three times daily, dose adjustments were considered twice weekly based on pre-prandial and bedtime SMPG from the preceding 3 days and the individualized goal according to investigator's discretion. Subjects were followed up for 5 weeks (week 57) for safety.

Reporting group title	Semaglutide

Reporting group description:

Subjects received metformin, IGlar U100 and semaglutide for 52 weeks in treatment period. Metformin dose was maintained at same level and frequency as optimized in run-in period unless safety concern related to background medication arose; IGlar U100 dose was adjusted in run-in period, increases in IGlar U100 dose was based on mean of 3 prebreakfast self-measured plasma glucose (SMPG) values obtained on day of visit/telephone contact and 2 days before contact and dose reduction of IGlar U100 was considered in accordance with approved local label to reduce risk of hypoglycaemia. Subjects self-administered s.c. injection of semaglutide at an initiation dose of 0.25 mg once weekly, after 4 weeks dose was increased to 0.5 mg, and 1 mg after at least 4 weeks to further improve glycaemic control, at investigator's discretion. Dose reduction from 1 to 0.5 mg was allowed in case of safety concern/unacceptable intolerability. Subjects were followed up for 5 weeks (week 57) for safety.

Serious adverse events	Insulin Aspart	Semaglutide	
Total subjects affected by serious adverse events			
subjects affected / exposed	84 / 864 (9.72%)	65 / 874 (7.44%)	
number of deaths (all causes)	1	12	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bowen's disease			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory pseudotumour			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papilloma of breast			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to gastrointestinal tract			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian cancer			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal neoplasm			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma recurrent			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (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			
Hernia repair			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of internal fixation			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic procedure			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toe amputation			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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			
Adhesion			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Impaired healing			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular stent stenosis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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			
Asthma			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (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	1 / 864 (0.12%)	0 / 874 (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	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Electric shock			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	2 / 864 (0.23%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (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	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrong product administered			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	4 / 864 (0.46%)	3 / 874 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	2 / 864 (0.23%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	2 / 864 (0.23%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			

subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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	3 / 864 (0.35%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 864 (0.12%)	2 / 874 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 864 (0.12%)	4 / 874 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	3 / 864 (0.35%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	4 / 864 (0.46%)	2 / 874 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			

subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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			
Iron deficiency anaemia			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	3 / 864 (0.35%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Optic ischaemic neuropathy			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal polyp			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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	2 / 864 (0.23%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Jaundice cholestatic			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder perforation			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 864 (0.00%)	3 / 874 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Facet joint syndrome			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess sweat gland			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			

subjects affected / exposed	2 / 864 (0.23%)	3 / 874 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Diabetic gangrene			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gangrene			
subjects affected / exposed	0 / 864 (0.00%)	3 / 874 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 864 (0.58%)	3 / 874 (0.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 864 (0.00%)	2 / 874 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 864 (0.23%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal abscess			

subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 864 (0.12%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	2 / 864 (0.23%)	1 / 874 (0.11%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia unawareness			
subjects affected / exposed	1 / 864 (0.12%)	0 / 874 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 864 (0.00%)	1 / 874 (0.11%)	
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	Insulin Aspart	Semaglutide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 864 (7.52%)	225 / 874 (25.74%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 864 (2.55%)	65 / 874 (7.44%)	
occurrences (all)	29	98	
Nausea			
subjects affected / exposed	7 / 864 (0.81%)	129 / 874 (14.76%)	
occurrences (all)	7	174	
Vomiting			
subjects affected / exposed	5 / 864 (0.58%)	50 / 874 (5.72%)	
occurrences (all)	6	78	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	51 / 864 (5.90%)	57 / 874 (6.52%)	
occurrences (all)	73	69	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported