Clinical trial results:
A trial comparing the efficacy and safety of insulin degludec and insulin glargine 300 units/mL in subjects with type 2 diabetes mellitus inadequately treated with basal insulin with or without oral antidiabetic drugs

Summary

EudraCT number	2016-002801-20
Trial protocol	DE HU DK EE GR PL
Global end of trial date	04 March 2019

Results information

Result version number	v1 (current)
This version publication date	26 February 2020
First version publication date	26 February 2020

Trial information

Trial identification

Sponsor protocol code	NN1250-4252

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03078478
WHO universal trial number (UTN)	U1111-1184-8175

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.ccom
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.ccom

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	10 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2019
Global end of trial reached?	Yes
Global end of trial date	04 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of insulin degludec once daily and insulin glargine 300 units/mL once daily on hypoglycaemia in subjects with type 2 diabetes mellitus, inadequately treated with basal insulin with or without oral anti-diabetic drugs.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th WMA General Assembly, October 2013) and ICH Good Clinical Practice, including archiving of essential documents, (June 1996) and 21 CFR 312.120.

Background therapy:

The participants were previously treated with basal insulin once daily or twice daily ± oral anti-diabetic drugs excluding sulfonylureas/glinides. Pre-trial insulin was discontinued and the subjects continued their pre-trial OADs.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	13 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 87
Country: Number of subjects enrolled	Germany: 100
Country: Number of subjects enrolled	Denmark: 32
Country: Number of subjects enrolled	Estonia: 40
Country: Number of subjects enrolled	Greece: 58
Country: Number of subjects enrolled	Hungary: 62
Country: Number of subjects enrolled	Norway: 20
Country: Number of subjects enrolled	Poland: 145
Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	Serbia: 60
Country: Number of subjects enrolled	United States: 984
Worldwide total number of subjects	1609
EEA total number of subjects	478

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)	836
From 65 to 84 years	764
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 230 sites in 11 countries as follows. Number of sites that screened and randomised participants to treatment are given in parenthesis. Canada:(9/9), Denmark: (6/6), Estonia: (5/5), Germany: (11 /11), Greece: (7/7), Hungary: (9/9), Norway: (4/4), Poland: (9/9), Romania: (5/4), Serbia: (8/8), United States: (157/153).

Pre-assignment

Screening details:

The participants were previously treated with basal insulin once daily or twice daily ± oral anti-diabetic drugs excluding sulfonylureas/glinides. Pre-trial insulin was discontinued and the subjects continued their pre-trial OADs.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin degludec U200

Arm description:

Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

Arm type	Experimental
Investigational medicinal product name	INSULIN DEGLUDEC
Investigational medicinal product code	
Other name	Tresiba® 200 units/ml
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec 200 units/mL was administered once daily as subcutaneous injections in the thigh, upper arm or abdomen. The daily basal insulin dose was reduced by 20% from their pre-trial dose. Insulin dose was adjusted once weekly by the investigator, based on the mean of three fasting SMPG values, to reach a SMPG of 4.0-5.0 mmol/L (71-90 mg/dL).

Arm title	Insulin glargine U300

Arm description:

Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

Arm type	Active comparator
Investigational medicinal product name	INSULIN GLARGINE
Investigational medicinal product code	
Other name	Toujeo® 300 units/ml
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine (IGlar) 300 units/mL was administered once daily as subcutaneous injections in the thigh, upper arm or abdomen. The dose of IGlar U300 corresponded to the pre-trial daily basal insulin dose. Insulin dose was adjusted once weekly by the investigator, based on the mean of three fasting

SMPG values, to reach a SMPG of 4.0-5.0 mmol/L (71-90 mg/dL).

Number of subjects in period 1	Insulin degludec U200	Insulin glargine U300
Started	805	804
Completed	733	734
Not completed	72	70
Consent withdrawn by subject	54	49
Death	7	9
Unclassified	1	2
Lost to follow-up	10	10

Baseline characteristics

Reporting groups	
Reporting group title	Insulin degludec U200
Reporting group description:	
Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.	
Reporting group title	Insulin glargine U300
Reporting group description:	
Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.	

Reporting group values	Insulin degludec U200	Insulin glargine U300	Total
Number of subjects	805	804	1609
Age Categorical Units: Subjects			
Adults (18-64 years)	418	418	836
Adults (65-74 years)	301	308	609
From 75-84 years	82	73	155
85 years and over	4	5	9
Age Continuous Units: years			
arithmetic mean	62.9	62.8	
standard deviation	± 10	± 10	-
Gender Categorical Units: Subjects			
Female	333	368	701
Male	472	436	908

End points

End points reporting groups

Reporting group title	Insulin degludec U200

Reporting group description:

Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

Reporting group title	Insulin glargine U300

Reporting group description:

Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

Primary: Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point title	Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point description:

Severe or BG confirmed symptomatic hypoglycaemia was evaluated during maintenance 2 (36 weeks) period. Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

End point type	Primary

End point timeframe:

During maintenance 2 (36 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742	741		
Units: Rate of hypoglycaemic episodes				
number (not applicable)	216.8	243.9		

Statistical analyses

Statistical analysis title	Analysis 1

Statistical analysis description:

The number of episodes is analysed using a negative binomial regression model (log link) with the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model includes treatment, number of OADs, region, sex and dosing time as fixed factors, and age as a covariate. Missing values are imputed through multiple imputation by treatment arm, based on a Poisson model.

Comparison groups	Insulin degludec U200 v Insulin glargine U300

Number of subjects included in analysis	1483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1715
Method	Negative binomial regression
Parameter estimate	Treatment rate ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.06

Secondary: Basal insulin dose (units)

End point title	Basal insulin dose (units)

End point description:

The observed mean daily basal insulin doses was evaluated at the end of trial (88 weeks).

End point type	Secondary

End point timeframe:

At end of treatment (up to 88 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	703	704		
Units: Units				
arithmetic mean (standard deviation)	66.6 (± 48.54)	73.0 (± 48.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point title	Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point description:

Nocturnal severe or BG confirmed symptomatic hypoglycaemia was evaluated at the end of trial (88 weeks). The nocturnal period defined as the period between 00:01 and 05:59 a.m. (both inclusive). Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

End point type	Secondary

End point timeframe:

During maintenance 2 (36 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742	741		
Units: Rate of hypoglycaemic episodes				
number (not applicable)	62.30	93.75		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of severe hypoglycaemic episodes

End point title	Number of severe hypoglycaemic episodes

End point description:

Severe hypoglycaemia are those episodes positively adjudicated by the event adjudication committee according to the ADA definition of a severe hypoglycaemic episode. This was evaluated for maintenance 2 period. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

End point type	Secondary

End point timeframe:

During maintenance 2 (36 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	742	741		
Units: Rate of hypoglycaemic episodes				
number (not applicable)	0.98	4.88		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change in glycosylated haemoglobin (HbA1c) was evaluated from baseline to end of treatment period (week 88).

End point type	Secondary

End point timeframe:

From baseline to end of treatment (up to 88 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	694	700		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-0.54 (± 0.91)	-0.46 (± 0.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycaemia: Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point title	Hypoglycaemia: Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point description:

Severe or BG confirmed symptomatic hypoglycaemia was evaluated during treatment (up to 88 weeks). Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

End point type	Secondary

End point timeframe:

During treatment (up to 88 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	802	798		
Units: Rate of hypoglycaemic episodes				
number (not applicable)	137.8	163.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycaemia: Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point title	Hypoglycaemia: Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point description:

Nocturnal severe or BG confirmed symptomatic hypoglycaemia was evaluated at the end of trial (88 weeks). The nocturnal period defined as the period between 00:01 and 05:59 a.m. (both inclusive). Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

End point type	Secondary

End point timeframe:

During treatment (up to 88 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	802	798		
Units: Rate of hypoglycaemic episodes				
number (not applicable)	36.93	60.03		

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycaemia: Number of severe hypoglycaemic episodes

End point title	Hypoglycaemia: Number of severe hypoglycaemic episodes

End point description:

Severe hypoglycaemia are those episodes positively adjudicated by the event adjudication committee according to the ADA definition of a severe hypoglycaemic episode. This was evaluated for the total trial period (88 weeks). The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

End point type	Secondary

End point timeframe:

During treatment (up to 88 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	802	798		
Units: Rate of hypoglycaemic episodes				
number (not applicable)	2.06	5.21		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events

End point title	Number of adverse events

End point description:

The adverse events presented are treatment emergent. A treatment-emergent AE (TEAE) was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last days of randomised treatment or had onset date before the first day of exposure on randomised treatment and increased in severity during the treatment period and until 7 days after the last date of randomised treatment. Number of adverse events expressed in rates, from randomisation to end of maintenance period 2 (up to 88 weeks) is presented. Rate = number of events divided by patient years of exposure multiplied by 100.

End point type	Secondary

End point timeframe:

During treatment (up to 88 weeks)

End point values	Insulin degludec U200	Insulin glargine U300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	802	798		
Units: Rate of adverse events				
number (not applicable)	367.32	365.42		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first trial-related activity after the subject had signed the informed consent until the End of Trial (week 88) + 7 days follow-up period.

Adverse event reporting additional description:

A treatment-emergent adverse event was defined as one which had onset date on or after the 1st day of exposure to treatment and no later than 7 days after the last days of treatment or had onset date before the 1st day of exposure to treatment and increased in severity during the treatment period and until 7 days after the last date of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Insulin degludec U200

Reporting group description:

Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

Reporting group title	Insulin Glargine U300

Reporting group description:

Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

Serious adverse events	Insulin degludec U200	Insulin Glargine U300	
Total subjects affected by serious adverse events			
subjects affected / exposed	167 / 802 (20.82%)	141 / 798 (17.67%)	
number of deaths (all causes)	7	6	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder transitional cell carcinoma stage I			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer metastatic			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage IV			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal cancer metastatic			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal squamous cell carcinoma stage 0			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma stage IV			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer stage I			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.12%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal haemorrhage			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steal syndrome			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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			
Abdominal wall operation			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ablation			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric bypass			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenterostomy			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc operation			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal polypectomy			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device removal			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic surgery			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple drug therapy			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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			
Asthenia			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capsular contracture associated with breast implant			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	3 / 802 (0.37%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 interstitial pneumonitis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			

subjects affected / exposed	3 / 802 (0.37%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 802 (0.25%)	4 / 798 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus polyp			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Suicidal ideation			
subjects affected / exposed	2 / 802 (0.25%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood lactic acid increased			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arterial bypass occlusion			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug administered in wrong device			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 802 (0.37%)	3 / 798 (0.38%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal procedural complication			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haemorrhage			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional product misuse			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural oedema			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pulmonary embolism			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory failure			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypertension			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural nausea			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 802 (0.12%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Vitello-intestinal duct remnant			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	6 / 802 (0.75%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 802 (0.37%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina unstable			
subjects affected / exposed	6 / 802 (0.75%)	4 / 798 (0.50%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	9 / 802 (1.12%)	5 / 798 (0.63%)	
occurrences causally related to treatment / all	1 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 802 (0.25%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 802 (0.12%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	6 / 802 (0.75%)	3 / 798 (0.38%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			

subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	10 / 802 (1.25%)	5 / 798 (0.63%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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	2 / 802 (0.25%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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	1 / 802 (0.12%)	4 / 798 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypokinesia			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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			
Ataxia			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery disease			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cervical radiculopathy			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	3 / 802 (0.37%)	9 / 798 (1.13%)	
occurrences causally related to treatment / all	4 / 4	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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	5 / 802 (0.62%)	4 / 798 (0.50%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 802 (0.37%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	3 / 802 (0.37%)	5 / 798 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 802 (0.37%)	4 / 798 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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			
subjects affected / exposed	3 / 802 (0.37%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Blindness unilateral			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haematoma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular degeneration			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy proliferative			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhegmatogenous retinal detachment			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous adhesions			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	3 / 802 (0.37%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic duct dilatation			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peptic ulcer perforation			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stasis dermatitis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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			
Acute kidney injury			
subjects affected / exposed	4 / 802 (0.50%)	8 / 798 (1.00%)	
occurrences causally related to treatment / all	0 / 4	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder prolapse			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 802 (0.25%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyuria			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal mass			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid mass			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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			
Arthralgia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myofascial pain syndrome			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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	2 / 802 (0.25%)	5 / 798 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteopenia			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	2 / 802 (0.25%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 802 (0.25%)	3 / 798 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	3 / 802 (0.37%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 802 (0.12%)	3 / 798 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter infection			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 802 (0.37%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	0 / 802 (0.00%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parametritis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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	6 / 802 (0.75%)	9 / 798 (1.13%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 802 (0.12%)	2 / 798 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (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	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Streptococcal sepsis			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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	2 / 802 (0.25%)	5 / 798 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 802 (0.25%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 802 (0.12%)	0 / 798 (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	1 / 802 (0.12%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 802 (0.37%)	0 / 798 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	8 / 802 (1.00%)	19 / 798 (2.38%)	
occurrences causally related to treatment / all	7 / 8	18 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 802 (0.12%)	1 / 798 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 802 (0.00%)	1 / 798 (0.13%)	
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 degludec U200	Insulin Glargine U300	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	496 / 802 (61.85%)	476 / 798 (59.65%)	
Nervous system disorders			
Headache			
subjects affected / exposed	51 / 802 (6.36%)	62 / 798 (7.77%)	
occurrences (all)	61	70	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	72 / 802 (8.98%)	79 / 798 (9.90%)	
occurrences (all)	90	97	
Nausea			
subjects affected / exposed	43 / 802 (5.36%)	50 / 798 (6.27%)	
occurrences (all)	53	56	
Vomiting			
subjects affected / exposed	26 / 802 (3.24%)	40 / 798 (5.01%)	
occurrences (all)	30	52	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	48 / 802 (5.99%)	46 / 798 (5.76%)	
occurrences (all)	60	53	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	51 / 802 (6.36%)	65 / 798 (8.15%)	
occurrences (all)	59	84	
Back pain			
subjects affected / exposed	59 / 802 (7.36%)	62 / 798 (7.77%)	
occurrences (all)	73	70	
Pain in extremity			
subjects affected / exposed	45 / 802 (5.61%)	43 / 798 (5.39%)	
occurrences (all)	49	49	
Infections and infestations			
Bronchitis			
subjects affected / exposed	48 / 802 (5.99%)	46 / 798 (5.76%)	
occurrences (all)	54	46	
Influenza			
subjects affected / exposed	59 / 802 (7.36%)	41 / 798 (5.14%)	
occurrences (all)	64	44	
Nasopharyngitis			
subjects affected / exposed	152 / 802 (18.95%)	161 / 798 (20.18%)	
occurrences (all)	253	265	
Sinusitis			
subjects affected / exposed	45 / 802 (5.61%)	40 / 798 (5.01%)	
occurrences (all)	58	53	
Upper respiratory tract infection			
subjects affected / exposed	145 / 802 (18.08%)	122 / 798 (15.29%)	
occurrences (all)	199	177	
Urinary tract infection			
subjects affected / exposed	49 / 802 (6.11%)	47 / 798 (5.89%)	
occurrences (all)	58	65	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2018	Due to an unusual data reporting pattern of hypoglycaemia and glycaemic values being linked to the glycaemic data collection system (the combined use of MyGlucoHealth with the eDiary) it was decided on 13-Feb-2018 to apply a new data collecting system consisting of an Abbott BGM and paper diary. To accommodate changes in the data collection system and to ensure sufficient data collection with respect to the confirmatory endpoints a new maintenance period (maintenance 2) of 36 weeks duration was included in the trial.

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/30974986