Clinical trial results:
Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting. A 104-week randomised, phase 4, two-arm, open-label, active-controlled, multicentre, multinational, parallel-group trial.

Summary

EudraCT number	2015-002417-29
Trial protocol	LV
Global end of trial date	12 August 2019

Results information

Result version number	v1 (current)
This version publication date	19 August 2020
First version publication date	19 August 2020

Trial information

Trial identification

Sponsor protocol code	NN2211-4232

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02730377
WHO universal trial number (UTN)	U1111-1170-7035

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2019
Global end of trial reached?	Yes
Global end of trial date	12 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. oral antidiabetic drugs (OADs) as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes (T2D) treated in primary care, inadequately controlled with metformin monotherapy.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice including archiving of essential document.

Background therapy:

Subjects were to continue their pre-trial metformin treatment maintained at the pre-trial dose and frequency during the entire trial treatment period unless there was a safety concern.

Evidence for comparator:

Not applicable

Actual start date of recruitment	28 March 2016
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	Latvia: 30
Country: Number of subjects enrolled	Canada: 102
Country: Number of subjects enrolled	Colombia: 30
Country: Number of subjects enrolled	India: 207
Country: Number of subjects enrolled	Lebanon: 20
Country: Number of subjects enrolled	Russian Federation: 85
Country: Number of subjects enrolled	Serbia: 60
Country: Number of subjects enrolled	Turkey: 33
Country: Number of subjects enrolled	United States: 1424
Worldwide total number of subjects	1991
EEA total number of subjects	30

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)	1490
From 65 to 84 years	495
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 219 sites in Canada (11), Colombia (3), India (16), Latvia (2), Lebanon (4), Russian Federation (5), Serbia (6), Turkey (4) and the United States (168).

Pre-assignment

Screening details:

Subjects were randomised in a 1:1 manner to receive either liraglutide or an oral antidiabetic drug (OAD) both as add-on to background therapy with metformin.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide 1.8 mg

Arm description:

Subjects were to receive a subcutaneous injection of liraglutide once daily. Subjects received 0.6 milligrams (mg) liraglutide during the first week. The dose was escalated in weekly increments of 0.6 mg until the dose of 1.8 mg was reached. The treatment period was 104 weeks.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received s.c. injection of 0.6 mg liraglutide during the first week. The dose was escalated in weekly increments of 0.6 mg until the dose of 1.8 mg was reached. A maintenance dose of 1.2 mg was accepted if the subject's HbA1c was < 7.0% (53 millimoles per mole [mmol/mol]), however, escalation to 1.8 mg was to be attempted if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Arm title	Oral antidiabetic drug

Arm description:

Subjects were to receive one selected OAD. The following OADs were allowed: alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulfonylureas or thiazolidinediones. The treatment period was 104 weeks.

Arm type	Active comparator
Investigational medicinal product name	Sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received sitagliptin 100 mg tablets once daily. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5 mg of linagliptin in total during the treatment period. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Saxagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5 mg of saxagliptin per day orally. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Vildagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg of vildagliptin per day orally. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 10 mg of dapagliflozin per day orally. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 25 mg of empagliflozin per day orally. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum

approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Gliclazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 120 mg of gliclazide per day orally. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 6 mg of glimepiride per day orally. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 45 mg of pioglitazone per day orally. The dose was escalated to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose was acceptable if the subject's HbA1c was <7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose was to be attempted, at the discretion of the investigator, if the subjects' HbA1c was ≥ 7% (53 mmol/mol).

Number of subjects in period 1	Liraglutide 1.8 mg	Oral antidiabetic drug
Started	996	995
Treated	980	984
Full analysis set (FAS)	996	995
Safety analysis set (SAS)	980	984
Completed	446	362
Not completed	550	633
Adverse event, serious fatal	1	8
Consent withdrawn by subject	45	42
Adverse event, non-fatal	79	41
Pregnancy	-	1

Inadequate glycaemic control	368	473
Unspecified	5	4
Lost to follow-up	25	21
Protocol deviation	23	30
Lack of efficacy	4	13

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide 1.8 mg
Reporting group description:	
Subjects were to receive a subcutaneous injection of liraglutide once daily. Subjects received 0.6 milligrams (mg) liraglutide during the first week. The dose was escalated in weekly increments of 0.6 mg until the dose of 1.8 mg was reached. The treatment period was 104 weeks.	
Reporting group title	Oral antidiabetic drug
Reporting group description:	
Subjects were to receive one selected OAD. The following OADs were allowed: alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulfonylureas or thiazolidinediones. The treatment period was 104 weeks.	

Reporting group values	Liraglutide 1.8 mg	Oral antidiabetic drug	Total
Number of subjects	996	995	1991
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	57.6	57.1	
standard deviation	± 11.0	± 10.7	-
Gender Categorical Units: Subjects			
Female	476	471	947
Male	520	524	1044

End points

End points reporting groups

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

Subjects were to receive a subcutaneous injection of liraglutide once daily. Subjects received 0.6 milligrams (mg) liraglutide during the first week. The dose was escalated in weekly increments of 0.6 mg until the dose of 1.8 mg was reached. The treatment period was 104 weeks.

Reporting group title	Oral antidiabetic drug

Reporting group description:

Subjects were to receive one selected OAD. The following OADs were allowed: alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulfonylureas or thiazolidinediones. The treatment period was 104 weeks.

Primary: Time to inadequate glycaemic control defined as HbA1c > 7.0% (53 mmol/mol) at two scheduled consecutive visits

End point title	Time to inadequate glycaemic control defined as HbA1c > 7.0% (53 mmol/mol) at two scheduled consecutive visits

End point description:

Inadequate glycaemic control was defined as glycosylated haemoglobin (HbA1c) of 7.0% (53 mmol/mol) or greater at two consecutive visits after the first 26 weeks of treatment and up to 104 weeks. 25%, median (50%) and 75% percentiles for the cumulative distribution function, are obtained from the Kaplan-Meier survival function. HbA1c was recorded at weeks 38, 52, 65, 78, 91 and 104. Results are based on the full analysis set (FAS) which included all randomised subjects. Number of subjects analysed = subjects with available data.

End point type	Primary

End point timeframe:

After the first 26 weeks of treatment and up to 104 weeks

End point values	Liraglutide 1.8 mg	Oral antidiabetic drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	416	547		
Units: Weeks				
median (inter-quartile range (Q1-Q3))	108.9 (37.7 to 99999)	64.9 (35.4 to 107.4)		

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Oral antidiabetic drug

Statistical analysis description:

Test for no treatment difference is based on using a generalised log-rank test for interval censored failure time data.

Comparison groups	Liraglutide 1.8 mg v Oral antidiabetic drug

Number of subjects included in analysis	963
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Secondary: Number of subjects who achieve (Yes/No): HbA1c ≤6.5% (48 mmol/mol)

End point title	Number of subjects who achieve (Yes/No): HbA1c ≤6.5% (48 mmol/mol)

End point description:

Subjects who achieved HbA1c ≤6.5% (yes/no) is presented. Results are based on the full analysis set (FAS) which included all randomised subjects.

End point type	Secondary

End point timeframe:

At 104 weeks or at premature treatment discontinuation

End point values	Liraglutide 1.8 mg	Oral antidiabetic drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	996	995		
Units: subjects				
Yes	255	162		
No	741	833		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who achieve (Yes/No): HbA1c ≤7.0% (53 mmol/mol) without weight gain

End point title	Number of subjects who achieve (Yes/No): HbA1c ≤7.0% (53 mmol/mol) without weight gain

End point description:

Subjects who achieved HbA1c ≤7.0% without weight gain (yes/no) is presented. Results are based on the full analysis set (FAS) which included all randomised subjects.

End point type	Secondary

End point timeframe:

At 104 weeks or at premature treatment discontinuation

End point values	Liraglutide 1.8 mg	Oral antidiabetic drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	996	995		
Units: subjects				
Yes	329	234		
No	667	761		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting plasma glucose (FPG)

End point title	Change from baseline in fasting plasma glucose (FPG)

End point description:

Change from baseline (week 0) in FPG at week 104 or at premature treatment discontinuation is presented. Results are based on the full analysis set (FAS) which included all randomised subjects. In the below table, n refer to number of subjects analysed per treatment arm.

End point type	Secondary

End point timeframe:

At 104 weeks or at premature treatment discontinuation

End point values	Liraglutide 1.8 mg	Oral antidiabetic drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	996	995		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Week 104 (n=418, 346)	-2.2 (± 2.65)	-1.2 (± 2.46)		
Premature treatment discontinuation (n=103, 78)	-0.6 (± 2.91)	-0.6 (± 3.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight

End point title	Change from baseline in body weight

End point description:

Change from baseline (week 0) in body weight at week 104 or at premature treatment discontinuation is presented. Results are based on the full analysis set (FAS) which included all randomised subjects. In the below table, n refer to number of subjects analysed per treatment arm.

End point type	Secondary

End point timeframe:

At 104 weeks or at premature treatment discontinuation

End point values	Liraglutide 1.8 mg	Oral antidiabetic drug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	996	995		
Units: Kilogram (Kg)				
arithmetic mean (standard deviation)				
Change at week 104 (n=427, 349)	-3.8 (± 6.38)	-3.5 (± 6.19)		
Premature treatment discontinuation (n=116, 86)	-2.9 (± 3.74)	-2.2 (± 4.93)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Weeks 0-105

Adverse event reporting additional description:

All presented AEs are TEAEs. A TEAE was defined as an event that had onset date on or after the first day of exposure to trial product and no later than 7 days after the last day of trial product administration. Results are based on the SAS which included all participants exposed to at least one dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Oral antidiabetic drug

Reporting group description:

Subjects were to receive one selected OAD. The following OADs were allowed: alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulfonylureas or thiazolidinediones. The treatment period was 104 weeks.

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

Subjects were to receive a subcutaneous injection of liraglutide once daily. Subjects received 0.6 milligrams (mg) liraglutide during the first week. The dose was escalated in weekly increments of 0.6 mg until the dose of 1.8 mg was reached. The treatment period was 104 weeks.

Serious adverse events	Oral antidiabetic drug	Liraglutide 1.8 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 984 (8.23%)	92 / 980 (9.39%)	
number of deaths (all causes)	8	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer metastatic			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage IV			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			

subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural mesothelioma malignant			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer stage III			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Triple negative breast cancer			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			

subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 984 (0.20%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 984 (0.20%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
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	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary artery bypass			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrectomy			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic surgery			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal laminectomy			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
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	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 984 (0.10%)	4 / 980 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Completed suicide			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Conversion disorder			
subjects affected / exposed	0 / 984 (0.00%)	2 / 980 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusional disorder, unspecified type			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin increased			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications				
Ankle fracture				
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	0 / 984 (0.00%)	1 / 980 (0.10%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Concussion				
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Fall				
subjects affected / exposed	2 / 984 (0.20%)	1 / 980 (0.10%)		
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	2 / 984 (0.20%)	0 / 980 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gun shot wound				
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Hip fracture				
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Humerus fracture				
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Joint dislocation				

subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
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	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	6 / 984 (0.61%)	5 / 980 (0.51%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 984 (0.10%)	4 / 980 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 984 (0.20%)	3 / 980 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	4 / 984 (0.41%)	3 / 980 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 984 (0.20%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 984 (0.20%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 984 (0.10%)	4 / 980 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 984 (0.00%)	2 / 980 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			

subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord haematoma			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 984 (0.20%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			

subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
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	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exophthalmos			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis ischaemic			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	2 / 984 (0.20%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			

subjects affected / exposed	2 / 984 (0.20%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 984 (0.20%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatosplenomegaly			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	2 / 984 (0.20%)	6 / 980 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 984 (0.00%)	2 / 980 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			

subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 984 (0.20%)	2 / 980 (0.20%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Empty sella syndrome			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
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			
Back pain			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc displacement			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 984 (0.00%)	2 / 980 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 984 (0.00%)	2 / 980 (0.20%)	
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	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 984 (0.10%)	3 / 980 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
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 / 984 (0.00%)	1 / 980 (0.10%)	
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 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (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	5 / 984 (0.51%)	4 / 980 (0.41%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 984 (0.30%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tonsillitis			

subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 984 (0.10%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			

subjects affected / exposed	1 / 984 (0.10%)	0 / 980 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 984 (0.00%)	1 / 980 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	1 / 984 (0.10%)	2 / 980 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Oral antidiabetic drug	Liraglutide 1.8 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 984 (1.52%)	65 / 980 (6.63%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 984 (1.52%)	65 / 980 (6.63%)	
occurrences (all)	21	82	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2016	It included updates to drug accountability, inclusion criterion number 4, statistical section and other clarifications and minor updates. Inclusion criteria-4: Stable daily dose of metformin as monotherapy ≥1500 mg or maximum tolerated dose for ≥60 days prior to the screening visit.

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/6617804