Clinical trial results:
A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus

Summary

EudraCT number	2017-003490-33
Trial protocol	SK GR AT HU PL ES IT RO
Global end of trial date	10 October 2019

Results information

Result version number	v1 (current)
This version publication date	13 June 2020
First version publication date	13 June 2020

Trial information

Trial identification

Sponsor protocol code	H9X-MC-GBGL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03495102
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16877

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of investigational doses of once weekly dulaglutide when added to metformin in participants with type 2 diabetes with inadequate blood sugar control.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 290
Country: Number of subjects enrolled	Romania: 233
Country: Number of subjects enrolled	Hungary: 73
Country: Number of subjects enrolled	United States: 508
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Greece: 100
Country: Number of subjects enrolled	Canada: 35
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Poland: 167
Country: Number of subjects enrolled	Mexico: 111
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Slovakia: 131
Country: Number of subjects enrolled	Israel: 54
Worldwide total number of subjects	1842
EEA total number of subjects	800

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)	1404
From 65 to 84 years	437
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

No Text Available

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Dulaglutide 1.5 mg

Arm description:

Dulaglutide 1.5 mg administered subcutaneously (SC) once a week.

Arm type	Active comparator
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	
Other name	LY2189265
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered SC

Arm title	Dulaglutide 3 mg

Arm description:

Dulaglutide 3 mg administered SC once a week.

Arm type	Experimental
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	
Other name	LY2189265
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered SC

Arm title	Dulaglutide 4.5 mg

Arm description:

Dulaglutide 4.5 mg administered SC once a week.

Arm type	Experimental
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	
Other name	LY2189265
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
Administered SC

Number of subjects in period 1	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg
Started	612	616	614
Received at least one dose of study drug	612	616	614
Completed	556	549	560
Not completed	56	67	54
Adverse event, serious fatal	3	4	4
Site Closure	3	1	2
Physician decision	2	-	2
Consent withdrawn by subject	25	36	18
Primary Care Physician Recommendation	-	1	-
Adverse event, non-fatal	5	7	10
Non-compliance	1	-	-
Relocated to Another Country	-	1	-
Participant Duplicated at Another Site	-	-	1
Lost to follow-up	15	16	17
Participant was in Rehabilitation	1	-	-
Protocol deviation	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dulaglutide 1.5 mg
Reporting group description:	
Dulaglutide 1.5 mg administered subcutaneously (SC) once a week.	
Reporting group title	Dulaglutide 3 mg
Reporting group description:	
Dulaglutide 3 mg administered SC once a week.	
Reporting group title	Dulaglutide 4.5 mg
Reporting group description:	
Dulaglutide 4.5 mg administered SC once a week.	

Reporting group values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg
Number of subjects	612	616	614
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.8	56.9	56.6
standard deviation	± 9.7	± 10.2	± 10.2
Gender categorical Units: Subjects			
Female	314	288	296
Male	298	328	318
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	30	26	32
Asian	13	18	14
Native Hawaiian or Other Pacific Islander	1	1	3
Black or African American	28	31	23
White	529	521	530
More than one race	11	19	12
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Argentina	96	97	97
Romania	77	78	78
Hungary	25	24	24
United States	169	169	170
Russia	9	10	10
Spain	19	20	19
Greece	33	34	33
Canada	12	11	12
Austria	4	4	5
Taiwan	5	5	5
Poland	56	56	55

Mexico	37	38	36
Italy	9	8	8
Slovakia	43	44	44
Israel	18	18	18
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	214	214	213
Not Hispanic or Latino	369	363	371
Unknown or Not Reported	29	39	30
Hemoglobin A1C (HbA1c) at Baseline			
HbA1c is measured primarily to identify average plasma glucose concentration over prolonged periods of time.			
Units: Percentage of HbA1c			
arithmetic mean	8.64	8.63	8.64
standard deviation	± 0.94	± 1.00	± 0.91

Reporting group values	Total		
Number of subjects	1842		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	898		
Male	944		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	88		
Asian	45		
Native Hawaiian or Other Pacific Islander	5		
Black or African American	82		
White	1580		
More than one race	42		
Unknown or Not Reported	0		
Region of Enrollment Units: Subjects			
Argentina	290		
Romania	233		
Hungary	73		
United States	508		
Russia	29		
Spain	58		
Greece	100		
Canada	35		
Austria	13		
Taiwan	15		
Poland	167		

Mexico	111		
Italy	25		
Slovakia	131		
Israel	54		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	641		
Not Hispanic or Latino	1103		
Unknown or Not Reported	98		
Hemoglobin A1C (HbA1c) at Baseline			
HbA1c is measured primarily to identify average plasma glucose concentration over prolonged periods of time.			
Units: Percentage of HbA1c			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Dulaglutide 1.5 mg
Reporting group description:	
Dulaglutide 1.5 mg administered subcutaneously (SC) once a week.	
Reporting group title	Dulaglutide 3 mg
Reporting group description:	
Dulaglutide 3 mg administered SC once a week.	
Reporting group title	Dulaglutide 4.5 mg
Reporting group description:	
Dulaglutide 4.5 mg administered SC once a week.	

Primary: Change in Hemoglobin A1c (HbA1c) from Baseline

End point title	Change in Hemoglobin A1c (HbA1c) from Baseline

End point description:

HbA1c is measured to identify average plasma glucose concentration over prolonged periods of time. The Least Squares (LS) mean was estimated from a mixed-effects model with repeated measures (MMRM) that included the independent variables:Baseline + Pooled Country + Treatment + Time + Treatment*Time (Type III sum of squares).

Analysis Population Description: All participants who received at least one dose of study drug and had a baseline and at least 1 post-baseline HbA1c value, excluding data post treatment discontinuation and/or initiation of new antihyperglycemic medications.

End point type	Primary

End point timeframe:

Baseline, Week 36

End point values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	523	521	526	
Units: Percentage of HbA1c				
least squares mean (standard error)	-1.53 (± 0.04)	-1.71 (± 0.04)	-1.87 (± 0.04)	

Statistical analyses

Statistical analysis title	Change in Hemoglobin A1c (HbA1c) from Baseline
Comparison groups	Dulaglutide 1.5 mg v Dulaglutide 3 mg

Number of subjects included in analysis	1044
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.06

Statistical analysis title	Change in Hemoglobin A1c (HbA1c) from Baseline
Comparison groups	Dulaglutide 1.5 mg v Dulaglutide 4.5 mg
Number of subjects included in analysis	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.22

Secondary: Change in Body Weight from Baseline

End point title	Change in Body Weight from Baseline

End point description:

Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with independent variables: Baseline + Baseline HbA1c group + Pooled Country + Treatment + Time + Treatment*Time (Type III sum of squares).

Analysis Population Description: All participants who received at least one dose of study drug and had a baseline and at least 1 post-baseline body weight value, excluding data post treatment discontinuation and/or initiation of new antihyperglycemic medications.

End point type	Secondary

End point timeframe:

Baseline, Week 36

End point values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	522	520	526	
Units: Kilograms (Kg)				
least squares mean (standard deviation)	-3.1 (± 0.19)	-4.0 (± 0.19)	-4.7 (± 0.19)	

Statistical analyses

Statistical analysis title	Change in Body Weight from Baseline
Comparison groups	Dulaglutide 3 mg v Dulaglutide 1.5 mg
Number of subjects included in analysis	1042
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.4

Statistical analysis title	Change in Body Weight from Baseline
Comparison groups	Dulaglutide 1.5 mg v Dulaglutide 4.5 mg
Number of subjects included in analysis	1048
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-1.1

Secondary: Percentage of Participants Achieving HbA1c Target <7.0%

End point title	Percentage of Participants Achieving HbA1c Target <7.0%

End point description:

Percentage of participants achieving HbA1c target <7.0%.

Analysis Population Description: All participants who received at least one dose of study drug and had a baseline and at least 1 post-baseline HbA1c value, excluding data post treatment discontinuation and/or initiation of new antihyperglycemic medications.

End point type	Secondary

End point timeframe:

Week 36

End point values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	523	521	526	
Units: percentage of participants				
number (not applicable)	56.98	64.68	71.48	

Statistical analyses

Statistical analysis title	Participants Achieving HbA1c Target <7.0%
Comparison groups	Dulaglutide 1.5 mg v Dulaglutide 3 mg
Number of subjects included in analysis	1044
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	1.98

Statistical analysis title	Participants Achieving HbA1c Target <7.0%
Comparison groups	Dulaglutide 1.5 mg v Dulaglutide 4.5 mg
Number of subjects included in analysis	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	3.01

Secondary: Change in Fasting Serum Glucose (FSG) from Baseline	
End point title	Change in Fasting Serum Glucose (FSG) from Baseline

End point description:

Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with covariates: Baseline + Baseline HbA1c group + Pooled Country + Treatment + Time + Treatment*Time (Type III sum of squares).

Analysis Population Description: All participants who received at least one dose of study drug and had a baseline and at least 1 post-baseline FSG value, excluding data post treatment discontinuation and/or initiation of new antihyperglycemic medications.

End point type	Secondary

End point timeframe:

Baseline, Week 36

End point values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	510	509	514	
Units: milligrams per deciliter (mg/dL)				
least squares mean (standard error)	-44.2 (± 1.50)	-47.9 (± 1.50)	-52.3 (± 1.50)	

Statistical analyses

Statistical analysis title	Change in FSG From Baseline
Comparison groups	Dulaglutide 1.5 mg v Dulaglutide 3 mg
Number of subjects included in analysis	1019
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	0.5

Statistical analysis title	Change in FSG From Baseline
Comparison groups	Dulaglutide 1.5 mg v Dulaglutide 4.5 mg

Number of subjects included in analysis	1024
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.3
upper limit	-3.9

Secondary: Rate of Documented Symptomatic Hypoglycemic Episodes

End point title	Rate of Documented Symptomatic Hypoglycemic Episodes

End point description:

Hypoglycemia was defined as blood glucose < 54 mg/dL, excluding post-rescue records. Estimate is based on Group Mean (Least Squares Mean was selected from the dropdown list because there is no Group Mean option) from negative binomial model. The negative binomial model for post-baseline comparisons between treatments and control group: Number of episodes = Pooled Country + HbA1c at Baseline (%) + Treatment, with log (exposure in days/365.25) as an offset variable.

Analysis Population Description: All participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Week 36

End point values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	612	616	614	
Units: Episodes/participant/365.25 days				
least squares mean (standard error)	0.02 (± 0.01)	0.00 (± 0.00)	0.02 (± 0.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK): Steady-state Maximum Concentration(Cmax,ss)

End point title	Pharmacokinetic (PK): Steady-state Maximum Concentration(Cmax,ss)

End point description:

Pharmacokinetic (PK): Steady-state Maximum Concentration(Cmax,ss).

Analysis Population Description: All participants who received at least one dose of study drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Week 4, Week 12, Week 36, Week 52, Week 56

End point values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	612	616	614	
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (confidence interval 90%)	79.6 (77.7 to 81.7)	159 (155 to 163)	238 (232 to 243)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK): Area Under the Curve AUC (0-168)ss at Steady State

End point title	Pharmacokinetic (PK): Area Under the Curve AUC (0-168)ss at Steady State

End point description:

Pharmacokinetic (PK): Area Under the Curve AUC (0-168)ss at Steady State.

All participants who received at least one dose of study drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Week 4, Week 12, Week 36, Week 52, Week 56

End point values	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	612	616	614	
Units: nanogram*hour/milliliter (ng*h/mL)				
arithmetic mean (confidence interval 90%)	11200 (10900 to 11500)	22300 (21800 to 22900)	33400 (32700 to 34200)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Week 56	
Adverse event reporting additional description: All participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Dulaglutide 1.5 mg
Reporting group description: Dulaglutide 1.5 mg administered subcutaneously (SC) once a week.	
Reporting group title	Dulaglutide 3 mg
Reporting group description: Dulaglutide 3 mg administered SC once a week.	
Reporting group title	Dulaglutide 4.5 mg
Reporting group description: Dulaglutide 4.5 mg administered SC once a week.	

Serious adverse events	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 612 (8.66%)	45 / 616 (7.31%)	38 / 614 (6.19%)
number of deaths (all causes)	3	4	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
adenocarcinoma pancreas			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bladder cancer recurrent			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
clear cell renal cell carcinoma			

alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung adenocarcinoma			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
metastases to abdominal cavity			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
metastatic uterine cancer			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[1]	1 / 314 (0.32%)	0 / 288 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
neuroendocrine tumour			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
papillary thyroid cancer			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
phaeochromocytoma			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
plasma cell myeloma			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
prostate cancer			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[2]	1 / 298 (0.34%)	0 / 328 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
uterine leiomyoma			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[3]	1 / 314 (0.32%)	0 / 288 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
arteriosclerosis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypertension			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypertensive emergency			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
cholecystectomy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
pregnancy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[4]	0 / 314 (0.00%)	2 / 288 (0.69%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
death			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
medical device site joint inflammation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
non-cardiac chest pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 612 (0.33%)	1 / 616 (0.16%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sudden death			
alternative dictionary used:			

MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Reproductive system and breast disorders			
cervical polyp			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[5]	0 / 314 (0.00%)	1 / 288 (0.35%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oedema genital			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ovarian cyst			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[6]	0 / 314 (0.00%)	0 / 288 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
acute respiratory failure			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	2 / 616 (0.32%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypersensitivity pneumonitis			

alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nasal polyps			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nasal septum deviation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
major depression			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
panic attack			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
stress			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal ideation			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
amylase increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ecg signs of myocardial ischaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
electrocardiogram t wave inversion			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lipase increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 612 (0.33%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
alcohol poisoning			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
comminuted fracture			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
contusion			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
exposure to toxic agent			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fall			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
femoral neck fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fibula fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hand fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

head injury			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
humerus fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
limb traumatic amputation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower limb fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lumbar vertebral fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
post procedural haemorrhage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
acute myocardial infarction			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	2 / 612 (0.33%)	2 / 616 (0.32%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
angina pectoris			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
arteriosclerosis coronary artery			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial fibrillation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 612 (0.49%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrioventricular block complete			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrioventricular block second degree			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardiac arrest			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

cardiac failure			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardiac failure congestive			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardio-respiratory arrest			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
congestive cardiomyopathy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
coronary artery disease			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
left ventricular failure			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 612 (0.16%)	2 / 616 (0.32%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
myocardial ischaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
balance disorder			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cerebral artery occlusion			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cerebrovascular accident			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diabetic mononeuropathy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic stroke			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	2 / 616 (0.32%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
loss of consciousness			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neuralgia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
subarachnoid haemorrhage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
wernicke's encephalopathy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood loss anaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombocytopenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
acute vestibular syndrome			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vertigo			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
eyelid oedema			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abdominal pain upper			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastric polyps			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haematochezia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemorrhoids			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

hiatus hernia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
mesenteric vein thrombosis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
obstructive pancreatitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pancreatitis acute			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
small intestinal obstruction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
cholecystitis acute			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	2 / 616 (0.32%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholelithiasis			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatic cirrhosis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
jaundice			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
jaundice cholestatic			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
portal vein thrombosis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
angioedema			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
rash maculo-papular			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nephrolithiasis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
goitre			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
intervertebral disc protrusion			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lumbar spinal stenosis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteoarthritis			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteoarthropathy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
plica syndrome			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
abscess limb			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abscess neck			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bronchitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
campylobacter infection			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholecystitis infective			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chronic sinusitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
herpes zoster			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infective exacerbation of chronic obstructive airways disease			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower respiratory tract infection			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 612 (0.16%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteomyelitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
perinephric abscess			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
periorbital cellulitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 612 (0.33%)	2 / 616 (0.32%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyelonephritis acute			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyoderma			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

renal abscess			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sepsis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
viral infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
west nile viral infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
diabetic ketoacidosis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoglycaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 612 (0.16%)	0 / 616 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyponatraemia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
type 2 diabetes mellitus			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 612 (0.00%)	1 / 616 (0.16%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

Non-serious adverse events	Dulaglutide 1.5 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 612 (25.49%)	190 / 616 (30.84%)	195 / 614 (31.76%)
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	48 / 612 (7.84%)	75 / 616 (12.18%)	70 / 614 (11.40%)
occurrences (all)	83	118	176
dyspepsia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	17 / 612 (2.78%)	33 / 616 (5.36%)	18 / 614 (2.93%)
occurrences (all)	26	56	35

nausea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	87 / 612 (14.22%)	99 / 616 (16.07%)	106 / 614 (17.26%)
occurrences (all)	121	180	192
vomiting			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	40 / 612 (6.54%)	57 / 616 (9.25%)	64 / 614 (10.42%)
occurrences (all)	63	89	108
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	29 / 612 (4.74%)	33 / 616 (5.36%)	39 / 614 (6.35%)
occurrences (all)	38	41	48

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported