Clinical trial results:
A 5-year study to compare the durability of glycemic control of a combination regimen with vildagliptin & metformin versus standard-of-care monotherapy with metformin, initiated in treatment-naïve patients with type 2 diabetes mellitus

Summary

EudraCT number	2011-003712-23
Trial protocol	LT FI LV IT HU DE EE SK BG PL NO CZ AT ES
Global end of trial date	04 April 2019

Results information

Result version number	v1 (current)
This version publication date	15 April 2020
First version publication date	15 April 2020

Trial information

Trial identification

Sponsor protocol code	CLAF237A23156

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01528254
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	04 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2019
Global end of trial reached?	Yes
Global end of trial date	04 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate the superiority of combination of vildagliptin 50mg bid and metformin over metformin monotherapy in treatment-naïve patients with T2DM by testing the hypothesis that the risk of confirmed initial treatment failure (defined as HbA1c ≥ 7.0%) is lower with the combination of vildagliptin and metformin compared to that with metformin monotherapy

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2012
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: 147
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Brazil: 59
Country: Number of subjects enrolled	Bulgaria: 108
Country: Number of subjects enrolled	Colombia: 51
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	Dominican Republic: 15
Country: Number of subjects enrolled	Estonia: 17
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Guatemala: 117
Country: Number of subjects enrolled	Hong Kong: 29
Country: Number of subjects enrolled	Hungary: 95
Country: Number of subjects enrolled	India: 163
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Korea, Republic of: 39

Country: Number of subjects enrolled	Latvia: 62
Country: Number of subjects enrolled	Lithuania: 46
Country: Number of subjects enrolled	Malaysia: 28
Country: Number of subjects enrolled	Mexico: 78
Country: Number of subjects enrolled	Norway: 17
Country: Number of subjects enrolled	Panama: 11
Country: Number of subjects enrolled	Peru: 59
Country: Number of subjects enrolled	Philippines: 64
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Romania: 79
Country: Number of subjects enrolled	Russian Federation: 166
Country: Number of subjects enrolled	Slovakia: 206
Country: Number of subjects enrolled	South Africa: 62
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	Turkey: 39
Worldwide total number of subjects	2001
EEA total number of subjects	823

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)	1710
From 65 to 84 years	291
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

It was planned to screen approximately 4000 patients in order to randomize 2000 patients. Actually, 2001 patients were randomized, 998 patients into the Vilda 50mg bid + metformin group and 1003 into the placebo + metformin group.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Vilda 50mg bid + metformin

Arm description:

vildagliptin (Vilda 50mg bid) + Metformin

Arm type	Active comparator
Investigational medicinal product name	Vildagliptin
Investigational medicinal product code	
Other name	LAF237
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet (50 mg oral) of vildagliptin in the morning and one tablet in the evening with or without food.

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

Dosage and administration details:

Twice daily (bid) regimen during or after meals at the same time as vildagliptin.

Arm title	Placebo + metformin

Arm description:

Placebo of vildagliptin (Vilda 50mg bid) + Metformin

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily (bid) regimen during or after meals at the same time as vildagliptin matching placebo.

Investigational medicinal product name	Placebo of vildagliptin
Investigational medicinal product code	
Other name	Placebo

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet (50 mg oral) of vildagliptin matching placebo in the morning and one tablet in the evening with or without food.

Number of subjects in period 1	Vilda 50mg bid + metformin	Placebo + metformin
Started	998	1003
Safety Set	998	1001
Full Analysis Set (FAS)	983	989
Completed Treatment Period 1	458 [1]	273 [2]
Completed Treatment Period 2	244 [3]	399 [4]
Completed Treatment Period 3	109 [5]	115 [6]
Completed	811	787
Not completed	187	216
Adverse event, serious fatal	13	9
Abnormal laboratory value(s)	3	7
Consent withdrawn by subject	5	4
Adverse event, non-fatal	28	44
Protocol deviation	9	19
Unsatisfactory therapeutic effect	6	8
Administrative problems	96	94
No longer requires study drug	1	1
Lost to follow-up	17	24
Abnormal test procedure result(s)	1	-
New therapy for study indication	8	6

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (treatment periods 1, 2 and 3)

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (treatment periods 1, 2 and 3)

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (treatment periods 1, 2 and 3)

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This was a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (treatment periods 1, 2 and 3)
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This was a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (treatment periods 1, 2 and 3)
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This was a multi-center, double-blind, placebo-controlled, 2-arm, parallel group study with a run-in period and up to 5 years treatment period (treatment periods 1, 2 and 3)

Baseline characteristics

Reporting groups	
Reporting group title	Vilda 50mg bid + metformin
Reporting group description: vildagliptin (Vilda 50mg bid) + Metformin	
Reporting group title	Placebo + metformin
Reporting group description: Placebo of vildagliptin (Vilda 50mg bid) + Metformin	

Reporting group values	Vilda 50mg bid + metformin	Placebo + metformin	Total
Number of subjects	998	1003	2001
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	854	856	1710
From 65-84 years	144	147	291
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	54.1	54.6	
standard deviation	± 9.54	± 9.24	-
Sex: Female, Male Units: Participants			
Female	545	515	1060
Male	453	488	941
Race/Ethnicity, Customized Units: Subjects			
Caucasian	605	612	1217
Black	26	23	49
Asian	186	187	373
Native American	103	107	210
Other	78	74	152
Glomerular Filtration Rate (Modification of Diet in Renal Disease)			
GFR (MDRD) = GFR estimated using the MDRD formula. Baseline GFR is calculated using the serum creatinine and body weight value at the Day 1 measurement, or the value obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing. Age is the value at screening.			
Units: Subjects			
Normal (>80)	660	661	1321
Mild (>=50 - <=80)	333	337	670
Moderate (>=30 - <50)	3	4	7

Severe (<30)	0	1	1
Missing	2	0	2
Is subject a current smoker?			
Smoking status is collected on the day of the screening measurement (Week -5, Visit 1)			
Units: Subjects			
Is subject a current smoker?=Yes	154	136	290
Is subject a current smoker?=No	844	867	1711
glycosylated hemoglobin (HbA1c)			
Baseline HbA1c is the sample obtained on day 1, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing.			
Units: Percent			
arithmetic mean	6.7	6.7	
standard deviation	± 0.45	± 0.47	-
fasting plasma glucose (FPG)			
Baseline FPG is the sample obtained on day 1, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing.			
Units: mmol/l			
arithmetic mean	7.1	7.2	
standard deviation	± 1.40	± 1.47	-
Duration of type 2 diabetes			
Duration of type 2 diabetes is collected on the day of the screening measurement (Week -5, Visit 1)			
Units: months			
arithmetic mean	6.2	6.6	
standard deviation	± 7.00	± 8.05	-

End points

End points reporting groups	
Reporting group title	Vilda 50mg bid + metformin
Reporting group description: vildagliptin (Vilda 50mg bid) + Metformin	
Reporting group title	Placebo + metformin
Reporting group description: Placebo of vildagliptin (Vilda 50mg bid) + Metformin	

Primary: Time to initial treatment failure

End point title	Time to initial treatment failure

End point description:

Treatment failure was defined as two consecutive scheduled visits with HbA1c >= 7.0% (starting from 13 weeks after randomization) and the time to treatment failure was the number of days from randomization to the second of the consecutive scheduled visits.
Participants who discontinued the study for any reason during Period 1 were censored at the date of discontinuation. Participants who remained under the threshold (or whose measurement above the threshold was not confirmed at next scheduled visit) were censored at the date of last study visit.

End point type	Primary

End point timeframe:

Visit 4 (Week 13) up to End of Study (Study Drug Discontinuation or Premature Subject Discontinuation)

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	983	989		
Units: Rate (%)				
number (confidence interval 95%)				
Weeks 13-52	7.81 (6.28 to 9.70)	19.97 (17.58 to 22.65)		
Year 2	17.79 (15.49 to 20.38)	34.67 (31.72 to 37.82)		
Year 3	31.24 (28.35 to 34.33)	48.31 (45.12 to 51.61)		
Year 4	39.84 (36.74 to 43.11)	59.29 (56.08 to 62.53)		
Year 5	46.41 (43.20 to 49.74)	66.57 (63.43 to 69.69)		
> Year 5	52.67 (44.29 to 61.58)	74.39 (68.39 to 80.04)		

Statistical analyses

Statistical analysis title	Time to initial treatment failure
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin

Number of subjects included in analysis	1972
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.58

Secondary: Rate of loss in glycemic control during Period 1

End point title	Rate of loss in glycemic control during Period 1

End point description:

The rate of loss in glycemic control was estimated using the slope of HbA1c over time (years). HbA1c data collected from Week 26 up to and including the end of Period 1 visit was included in the analysis. Baseline HbA1c was the sample obtained on day 1, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement was missing. End of Period 1 was defined as the final post-baseline assessment obtained at any visit within Period 1 (scheduled or unscheduled), up to the last scheduled visit.

End point type	Secondary

End point timeframe:

Visit 5 (Week 26) to End of Period 1

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	983	989		
Units: Rate (%)				
arithmetic mean (standard error)	0.24 (± 0.01)	0.27 (± 0.01)		

Statistical analyses

Statistical analysis title	Rate of loss in glycemic control (Period 1)
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	1972
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.042
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.01

Secondary: Rate of loss in glycemic control in HbA1c over time during Period 2

End point title	Rate of loss in glycemic control in HbA1c over time during Period 2

End point description:

The rate of loss in glycemic control was estimated using the slope of HbA1c over time (years). HbA1c data collected from 26 weeks after the start of Period 2 to the end of Period 2 were included in the analysis, for participants who started insulin therapy in Period 3 or discontinued during Period 2 due to being unable or unwilling to initiate insulin therapy in period 3. Participants who completed the study in Period 1 or Period 2 were not be included in the analysis.

End point type	Secondary

End point timeframe:

From 26 weeks after start of Period 2 to end of Period 2

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	588		
Units: Rate (%)				
arithmetic mean (standard error)	1.11 (± 0.15)	1.02 (± 0.12)		

Statistical analyses

Statistical analysis title	Rate loss in glycemic control in HbA1c (Period 2)
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.635
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: Rate of loss in glycemic control in Fasting Plasma Glucose (FPG) during Period 1

End point title	Rate of loss in glycemic control in Fasting Plasma Glucose (FPG) during Period 1

End point description:

Rate of loss in glycemic control was estimated using the slope of FPG over time (years).
FPG (fasting plasma glucose) data from Week 26 to the end of Period 1 was included in the analysis.
Baseline FPG was the sample obtained on day 1, or the sample obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurement is missing. Participants who completed the study in Period 1 or Period 2 were not be included in the analysis.

End point type	Secondary

End point timeframe:

Visit 5 (Week 26) to End of Period 1

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	983	989		
Units: Rate (%)				
arithmetic mean (standard error)	0.25 (± 0.01)	0.26 (± 0.01)		

Statistical analyses

Statistical analysis title	Rate of loss in glycemic control in FPG (Period 1)
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	1972
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.53
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.02

Secondary: Rate of loss in glycemic control in Fasting Plasma Glucose (FPG) over time during Period 2

End point title	Rate of loss in glycemic control in Fasting Plasma Glucose (FPG) over time during Period 2

End point description:

Rate of loss in glycemic control was estimated using the slope of FPG over time (years).
FPG (fasting plasma glucose) data from 26 weeks after the start of Period 2 to then end of Period 2 was included in the analysis. Only participants who started insulin therapy in Period 3 or discontinued during Period 2 due to being unable or unwilling to initiate insulin therapy in period 3 were included.
Participants who completed the study in Period 1 or Period 2 were not be included in the analysis.

End point type	Secondary

End point timeframe:

From 26 weeks after start of Period 2 to end of Period 2

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	588		
Units: Rate (%)				
arithmetic mean (standard error)	1.27 (± 0.25)	0.99 (± 0.19)		

Statistical analyses

Statistical analysis title	Rate of loss in glycemic control in FPG (Period 2)
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.381
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.32

Secondary: Rate of loss of beta cell function from baseline to end of study

End point title	Rate of loss of beta cell function from baseline to end of study

End point description:

The rate of change of beta cell function was assessed using the slope of AUC of ISR/G over time (years) where AUC of ISR/G is defined as (Area under curve of Insulin secretion rate (derived using c-peptide))/(Area under curve of Glucose), using meal-test data from 0 to 120 minutes. Baseline AUC of ISR/G was derived based on samples obtained on day 1, or samples obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurements were missing. Three analyses were included, using data from Week 13 to the end of Period 1, end of Period 2 and end of

respectively.

End point type	Secondary

End point timeframe:

Visit 4 (Week 13), End of Period 1, End of Period 2, End of Study (Study Drug Discontinuation or Premature Subject Discontinuation)

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	227		
Units: Rate (%)				
arithmetic mean (standard error)				
From Week 13 to end of Period 1	-0.60 (± 0.15)	-0.53 (± 0.18)		
From Week 13 to end of Period 2	-0.93 (± 0.14)	-0.43 (± 0.15)		
From Week 13 to end of study	-1.04 (± 0.15)	-0.46 (± 0.15)		

Statistical analyses

Statistical analysis title	Rate of loss of beta cell function
Statistical analysis description:	
From Week 13 to end of Period 1	
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.744
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.23

Statistical analysis title	Rate of loss of beta cell function
Statistical analysis description:	
From Week 13 to end of Period 2	
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin

Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.017
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.21

Statistical analysis title	Rate of loss of beta cell function
Statistical analysis description:	
From Week 13 to end of study	
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.21

Secondary: Rate of change in insulin sensitivity from baseline to end of study

End point title	Rate of change in insulin sensitivity from baseline to end of study

End point description:

The rate of change of insulin sensitivity is assessed using the slope of OGIS over time (years) where Oral glucose insulin sensitivity (OGIS) was calculated as a function of glucose and insulin, using meal-test data from 0 to 120 minutes. Baseline OGIS is derived based on samples obtained on day 1, or samples obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if the Day 1 measurements are missing. Three analyses were included, using data from Week 13 to the end of Period 1, end of Period 2 and end of study, respectively.

End point type	Secondary

End point timeframe:

Visit 4 (Week 13), End of Period 1, End of Period 2, End of Study (Study Drug Discontinuation or Premature Subject Discontinuation)

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	227		
Units: Rate (%)				
arithmetic mean (standard error)				
From Week 13 to end of Period 1	-4.61 (± 1.38)	0.41 (± 1.66)		
From Week 13 to end of Period 2	-6.07 (± 1.20)	-0.99 (± 1.24)		
From Week 13 to end of study	-6.39 (± 1.15)	-1.01 (± 1.17)		

Statistical analyses

Statistical analysis title	Rate of change in insulin sensitivity
Statistical analysis description: From Week 13 to end of Period 1	
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.02
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-5.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.26
upper limit	-0.79
Variability estimate	Standard error of the mean
Dispersion value	2.16

Statistical analysis title	Rate of change in insulin sensitivity
Statistical analysis description: From Week 13 to end of Period 2	
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-5.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.46
upper limit	-1.69
Variability estimate	Standard error of the mean
Dispersion value	1.73

Statistical analysis title	Rate of change in insulin sensitivity
Statistical analysis description:	
From Week 13 to end of study	
Comparison groups	Vilda 50mg bid + metformin v Placebo + metformin
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-5.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.61
upper limit	-2.16
Variability estimate	Standard error of the mean
Dispersion value	1.64

Secondary: Percentage of participants with adverse events, serious adverse events and death

End point title	Percentage of participants with adverse events, serious adverse events and death
End point description:	
Analysis of absolute and relative frequencies for treatment emergent Adverse Event (AE), Serious Adverse Event (SAE) and Deaths by primary System Organ Class (SOC) in each treatment arm to demonstrate that LAF237 is safe for the treatment of naïve patients with type 2 diabetes mellitus through the monitoring of relevant clinical and laboratory safety parameters.	
End point type	Secondary
End point timeframe:	
From first dose of study treatment until End of Study (Study Drug Discontinuation or Premature Subject Discontinuation)	

End point values	Vilda 50mg bid + metformin	Placebo + metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	998	1001		
Units: Percentage of Participants				
number (not applicable)				
On-treatment Adverse Event (AEs)	83.5	83.2		
On-treatment Serious Adverse Event (SAEs)	16.6	18.3		
On-treatment Deaths	1.3	0.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 75.6 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Vilda 50mg bid +@metformin

Reporting group description:

Vilda 50mg bid +@metformin

Reporting group title	Placebo +@metformin

Reporting group description:

Placebo +@metformin

Reporting group title	Total

Reporting group description:

Total

Serious adverse events	Vilda 50mg bid +@metformin	Placebo +@metformin	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	166 / 998 (16.63%)	183 / 1001 (18.28%)	349 / 1999 (17.46%)
number of deaths (all causes)	13	9	22
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Adenoma benign			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	3 / 998 (0.30%)	1 / 1001 (0.10%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer female			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choroid melanoma			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystadenocarcinoma ovary			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder neoplasm			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplasm			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal adenocarcinoma			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kaposi's sarcoma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Malignant melanoma			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant splenic neoplasm			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metastases to lung			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oligoastrocytoma			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer metastatic			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Ovarian epithelial cancer			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian neoplasm			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	3 / 998 (0.30%)	2 / 1001 (0.20%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Parathyroid tumour benign			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	6 / 998 (0.60%)	0 / 1001 (0.00%)	6 / 1999 (0.30%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectosigmoid cancer			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Refractory cytopenia with multilineage dysplasia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin papilloma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell carcinoma			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Undifferentiated sarcoma			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Aortic dissection			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	2 / 998 (0.20%)	4 / 1001 (0.40%)	6 / 1999 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			

subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion threatened			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy with contraceptive device			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Granuloma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical cyst			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial thickening			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital ulceration			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 998 (0.10%)	4 / 1001 (0.40%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian fibrosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatomegaly			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 998 (0.20%)	3 / 1001 (0.30%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cyst			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eating disorder			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIV test positive			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burns first degree			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat stroke			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 998 (0.10%)	4 / 1001 (0.40%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	0 / 1	1 / 4	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			

subjects affected / exposed	3 / 998 (0.30%)	0 / 1001 (0.00%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Muscle rupture			
subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fistula			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 998 (0.00%)	3 / 1001 (0.30%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Skin abrasion			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth fracture			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic arthrosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital intestinal malformation			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart disease congenital			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 998 (0.00%)	3 / 1001 (0.30%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute myocardial infarction			
subjects affected / exposed	3 / 998 (0.30%)	4 / 1001 (0.40%)	7 / 1999 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Angina pectoris			
subjects affected / exposed	2 / 998 (0.20%)	4 / 1001 (0.40%)	6 / 1999 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	6 / 998 (0.60%)	5 / 1001 (0.50%)	11 / 1999 (0.55%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block left			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	3 / 998 (0.30%)	4 / 1001 (0.40%)	7 / 1999 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure chronic			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Conduction disorder			

subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 998 (0.10%)	3 / 1001 (0.30%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Coronary artery insufficiency			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 998 (0.10%)	3 / 1001 (0.30%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve disease			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 998 (0.30%)	7 / 1001 (0.70%)	10 / 1999 (0.50%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	2 / 998 (0.20%)	3 / 1001 (0.30%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular extrasystoles			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular hypokinesia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 998 (0.00%)	4 / 1001 (0.40%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 998 (0.20%)	2 / 1001 (0.20%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular disorder			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Demyelination			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Ischaemic stroke			
subjects affected / exposed	2 / 998 (0.20%)	5 / 1001 (0.50%)	7 / 1999 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	3 / 998 (0.30%)	1 / 1001 (0.10%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytopenia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic anaemia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness neurosensory			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tinnitus			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric disorder			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric mucosal lesion			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal erosion			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal fistula			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 998 (0.20%)	0 / 1001 (0.00%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 998 (0.00%)	7 / 1001 (0.70%)	7 / 1999 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar hernia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal fibrosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 998 (0.10%)	4 / 1001 (0.40%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	4 / 998 (0.40%)	2 / 1001 (0.20%)	6 / 1999 (0.30%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	3 / 998 (0.30%)	1 / 1001 (0.10%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 998 (0.20%)	5 / 1001 (0.50%)	7 / 1999 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cyst			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic steatosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal syndrome			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocholecystis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer haemorrhage			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Bladder tamponade			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic nephropathy			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	3 / 998 (0.30%)	2 / 1001 (0.20%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			

subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 998 (0.00%)	3 / 1001 (0.30%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stag horn calculus			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoparathyroidism			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Exostosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty tophus			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	3 / 998 (0.30%)	2 / 1001 (0.20%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	1 / 3	0 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint contracture			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lumbar spinal stenosis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 998 (0.20%)	5 / 1001 (0.50%)	7 / 1999 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	1 / 998 (0.10%)	2 / 1001 (0.20%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudarthrosis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			

subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	3 / 998 (0.30%)	1 / 1001 (0.10%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	2 / 998 (0.20%)	2 / 1001 (0.20%)	4 / 1999 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bartholin's abscess			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone tuberculosis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic echinococciasis			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis viral			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			

subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis pneumococcal			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreas infection			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	14 / 998 (1.40%)	5 / 1001 (0.50%)	19 / 1999 (0.95%)
occurrences causally related to treatment / all	0 / 14	0 / 5	0 / 19
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pyelonephritis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			

subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 998 (0.10%)	1 / 1001 (0.10%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Subcutaneous abscess			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 998 (0.20%)	3 / 1001 (0.30%)	5 / 1999 (0.25%)
occurrences causally related to treatment / all	1 / 3	0 / 3	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral myelitis			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	2 / 998 (0.20%)	1 / 1001 (0.10%)	3 / 1999 (0.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 998 (0.00%)	2 / 1001 (0.20%)	2 / 1999 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 998 (0.00%)	1 / 1001 (0.10%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 998 (0.10%)	0 / 1001 (0.00%)	1 / 1999 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Vilda 50mg bid +@metformin	Placebo +@metformin	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	582 / 998 (58.32%)	566 / 1001 (56.54%)	1148 / 1999 (57.43%)
Vascular disorders			
Hypertension			
subjects affected / exposed	103 / 998 (10.32%)	124 / 1001 (12.39%)	227 / 1999 (11.36%)
occurrences (all)	116	130	246
Nervous system disorders			
Dizziness			
subjects affected / exposed	67 / 998 (6.71%)	41 / 1001 (4.10%)	108 / 1999 (5.40%)
occurrences (all)	99	61	160
Headache			

subjects affected / exposed	82 / 998 (8.22%)	72 / 1001 (7.19%)	154 / 1999 (7.70%)
occurrences (all)	120	107	227
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	104 / 998 (10.42%)	104 / 1001 (10.39%)	208 / 1999 (10.41%)
occurrences (all)	127	132	259
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	100 / 998 (10.02%)	94 / 1001 (9.39%)	194 / 1999 (9.70%)
occurrences (all)	115	124	239
Back pain			
subjects affected / exposed	105 / 998 (10.52%)	86 / 1001 (8.59%)	191 / 1999 (9.55%)
occurrences (all)	127	108	235
Osteoarthritis			
subjects affected / exposed	54 / 998 (5.41%)	40 / 1001 (4.00%)	94 / 1999 (4.70%)
occurrences (all)	60	44	104
Pain in extremity			
subjects affected / exposed	67 / 998 (6.71%)	74 / 1001 (7.39%)	141 / 1999 (7.05%)
occurrences (all)	81	89	170
Infections and infestations			
Bronchitis			
subjects affected / exposed	58 / 998 (5.81%)	59 / 1001 (5.89%)	117 / 1999 (5.85%)
occurrences (all)	87	79	166
Influenza			
subjects affected / exposed	93 / 998 (9.32%)	64 / 1001 (6.39%)	157 / 1999 (7.85%)
occurrences (all)	118	89	207
Nasopharyngitis			
subjects affected / exposed	104 / 998 (10.42%)	108 / 1001 (10.79%)	212 / 1999 (10.61%)
occurrences (all)	154	174	328
Upper respiratory tract infection			
subjects affected / exposed	83 / 998 (8.32%)	69 / 1001 (6.89%)	152 / 1999 (7.60%)
occurrences (all)	136	111	247
Urinary tract infection			
subjects affected / exposed	72 / 998 (7.21%)	69 / 1001 (6.89%)	141 / 1999 (7.05%)
occurrences (all)	96	87	183
Metabolism and nutrition disorders			

Dyslipidaemia subjects affected / exposed occurrences (all)	58 / 998 (5.81%) 62	71 / 1001 (7.09%) 72	129 / 1999 (6.45%) 134

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2011	Amendment no. 1 (released 27-Oct-2011): An additional meal-test was included for patients who were participating in the meal-test sub-study at Visit 4. This change, together with the additional meal-tests, enabled the evaluation of the rate of loss in β-cell function and the rate of change in insulin sensitivity based on the meal-test. Furthermore, clarification related to the timing of administration of the study drug at the visits when the meal-test was performed was inserted.
08 February 2012	Amendment no. 2 (released 08-Feb-2012): Additional clarification was included related to the occurrence of a contraindication against the treatment with metformin or vildagliptin during the study and to ensure only patients who received appropriate diet and exercise training with respect to lifestyle modifications prior to enrolment could be included.
04 October 2016	Amendment no. 3 (released 04-Oct-2016): The protocol was amended to accommodate the inclusion of an adjudication committee and a data monitoring committee (DMC), and to specify timelines for safety reporting. Furthermore, due to a metformin 500mg tablet variant introduced in the study with organoleptic properties which were not well perceived by subjects, the protocol now allowed the temporary use of commercial metformin 500mg tablets.
04 April 2019	Amendment no. 4 (released 22-Oct-2019): The protocol was amended based on a health authority request to incorporate the redefined order of analysis in the protocol to align with the final, published statistical analysis plan (published before LPLV; Matthews et al 2019b). The loss of glycaemic control was analysed as a secondary endpoint instead of a primary endpoint, and an additional detail was provided for the confirmatory visit for the primary analysis of time to initial treatment failure. Following this, only one primary endpoint approach was included in the statistical analysis plan analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported