



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess Cardiovascular Outcomes Following Treatment with MK-3102 in Subjects with Type 2 Diabetes Mellitus

Summary

EudraCT number	2012-002414-39
Trial protocol	HU NL DE NO SE AT CZ ES FI DK IT BE SK LT PL FR HR
Global end of trial date	22 March 2017

Results information

Result version number	v1 (current)
This version publication date	07 December 2017
First version publication date	07 December 2017

Trial information

Trial identification

Sponsor protocol code	MK-3102-018
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01703208
WHO universal trial number (UTN)	-
Other trial identifiers	MK-3102-018: Protocol number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialDisclosure@merck.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	22 March 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the cardiovascular (CV) safety profile of omarigliptin in participants with type 2 diabetes mellitus (T2DM). The primary hypothesis is that treatment with omarigliptin 25 mg once weekly is non-inferior to treatment with placebo and active comparators across the omarigliptin program with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Some participants in the Insulin Sub-study received insulin with or without metformin.

Evidence for comparator: -

Actual start date of recruitment	05 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 104
Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 61
Country: Number of subjects enrolled	Brazil: 94
Country: Number of subjects enrolled	Bulgaria: 73
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	Chile: 31
Country: Number of subjects enrolled	Colombia: 31
Country: Number of subjects enrolled	Croatia: 39
Country: Number of subjects enrolled	Czech Republic: 118
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Georgia: 403

Country: Number of subjects enrolled	Germany: 192
Country: Number of subjects enrolled	Hong Kong: 105
Country: Number of subjects enrolled	Hungary: 62
Country: Number of subjects enrolled	Israel: 29
Country: Number of subjects enrolled	Italy: 85
Country: Number of subjects enrolled	Korea, Republic of: 67
Country: Number of subjects enrolled	Lebanon: 57
Country: Number of subjects enrolled	Lithuania: 27
Country: Number of subjects enrolled	Malaysia: 99
Country: Number of subjects enrolled	Mexico: 24
Country: Number of subjects enrolled	Netherlands: 50
Country: Number of subjects enrolled	New Zealand: 60
Country: Number of subjects enrolled	Philippines: 88
Country: Number of subjects enrolled	Poland: 117
Country: Number of subjects enrolled	Romania: 195
Country: Number of subjects enrolled	Russian Federation: 143
Country: Number of subjects enrolled	Serbia: 79
Country: Number of subjects enrolled	Slovakia: 150
Country: Number of subjects enrolled	South Africa: 145
Country: Number of subjects enrolled	Spain: 183
Country: Number of subjects enrolled	Sweden: 29
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Ukraine: 192
Country: Number of subjects enrolled	United Kingdom: 55
Country: Number of subjects enrolled	United States: 845
Worldwide total number of subjects	4202
EEA total number of subjects	1518

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)	2211
From 65 to 84 years	1970
85 years and over	21

Subject disposition

Recruitment

Recruitment details:

A total of 559 sites received IEC/IRB approval in 40 countries and 547 were shipped clinical supplies. Of the 559 sites, 525 screened at least 1 participant. An insulin sub-study of MK-3102-018 was performed and included the sub-population of participants receiving ≥ 20 units/day of background insulin with or without metformin.

Pre-assignment

Screening details:

On April 8, 2016, Merck & Co. Inc. announced that it would not submit marketing applications for omarigliptin (MK-3102) in the US and Europe for business reasons only. Because of this decision, the MK-3102-018 study was terminated early on May 13, 2016 and due to delays in study close-out the Last-Participant-Last-Visit occurred on March 22, 2017.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Omarigliptin 25 mg

Arm description:

Omarigliptin (MK-3102) 25 mg capsule or tablet administered orally once weekly

Arm type	Experimental
Investigational medicinal product name	Omarigliptin (MK-3102) 25 mg capsule or tablet administered orally once weekly
Investigational medicinal product code	
Other name	MK-3102
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg capsule or tablet administered orally once weekly

Arm title	Placebo
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Arm description:

Matching placebo to omarigliptin capsule or tablet administered once weekly.

Arm type	Placebo
Investigational medicinal product name	Matching placebo to omarigliptin capsule or tablet administered once weekly
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Capsule or tablet administered once weekly

Number of subjects in period 1	Omarigliptin 25 mg	Placebo
Started	2100	2102
Treated	2092	2100
Completed	0	0
Not completed	2100	2102
Adverse event, serious fatal	61	48
Physician decision	11	13
Protocol Deviation	2	-
Site Discontinued Study Participation	23	27
Study Terminated by Sponsor	1710	1716
Consent withdrawn by subject	205	209
Non-Compliance with Study Drug	1	-
Excluded Medication	1	2
Adverse event, non-fatal	14	19
Technical Problems	-	1
Lost to follow-up	68	62
Progressive disease	2	2
Lack of efficacy	1	2
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Omarigliptin 25 mg
Reporting group description: Omarigliptin (MK-3102) 25 mg capsule or tablet administered orally once weekly	
Reporting group title	Placebo
Reporting group description: Matching placebo to omarigliptin capsule or tablet administered once weekly.	

Reporting group values	Omarigliptin 25 mg	Placebo	Total
Number of subjects	2100	2102	4202
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)	1118	1093	2211
From 65-84 years	970	1000	1970
85 years and over	12	9	21
Age Continuous Units: Years			
arithmetic mean	63.7	63.6	
standard deviation	± 8.5	± 8.5	-
Gender, Male/Female Units: Subjects			
Female	639	615	1254
Male	1461	1487	2948
Study Specific Characteristic Hemoglobin A1C %			
Hemoglobin A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%).			
Units: Percent			
arithmetic mean	7.99	8.03	
standard deviation	± 0.86	± 0.89	-
Study Specific Characteristic Fasting Plasma Glucose (FPG) Units: mg/dL			
arithmetic mean	184.1	179.5	
standard deviation	± 52.2	± 45.7	-

End points

End points reporting groups

Reporting group title	Omarigliptin 25 mg
Reporting group description:	Omarigliptin (MK-3102) 25 mg capsule or tablet administered orally once weekly
Reporting group title	Placebo
Reporting group description:	Matching placebo to omarigliptin capsule or tablet administered once weekly.

Primary: Number of Participants With MACE-plus (Confirmed Cardiovascular [CV]-Related Death, Nonfatal Myocardial Infarction [MI], Nonfatal Stroke, or Hospitalization Due to Unstable Angina)

End point title	Number of Participants With MACE-plus (Confirmed Cardiovascular [CV]-Related Death, Nonfatal Myocardial Infarction [MI], Nonfatal Stroke, or Hospitalization Due to Unstable Angina) ^[1]
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End point description:

Participants with confirmed MACE-plus events (confirmed cardiovascular, CV-related death, nonfatal myocardial infarction [MI], nonfatal stroke, or hospitalization due to unstable angina). In the MK-3102-018 study, MACE plus events had a data cut-off date of April 15, 2015. The analysis population included all randomized participants who took at least one dose of blinded study medication and were evaluated for MACE-plus events.

End point type	Primary
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End point timeframe:

Up to 156 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this end point.

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2090	2100		
Units: Participants	66	70		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With an Event of MACE (Confirmed CV-Related Death, Fatal and Nonfatal MI, and Fatal and Nonfatal Stroke)

End point title	Number of Participants With an Event of MACE (Confirmed CV-Related Death, Fatal and Nonfatal MI, and Fatal and Nonfatal Stroke) ^[2]
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End point description:

Participants with an Event of MACE (confirmed cardiovascular, CV-related death, fatal and nonfatal myocardial infarction [MI], and fatal and nonfatal stroke). The analysis population included all randomized participants who took at least one dose of blinded trial medication.

End point type	Primary
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End point timeframe:

Up to 179 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this end point.

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants	114	114		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with an Event Per 100 Person-Years for First Event of MACE (Confirmed CV-Related Death, Fatal and Nonfatal MI, and Fatal and Nonfatal Stroke)

End point title	Number of Participants with an Event Per 100 Person-Years for First Event of MACE (Confirmed CV-Related Death, Fatal and Nonfatal MI, and Fatal and Nonfatal Stroke)
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End point description:

Participants with an event of MACE (confirmed cardiovascular, CV-related death, fatal and nonfatal myocardial infarction [MI], and fatal and nonfatal stroke). Person-years were calculated as the sum of all participants' follow-up time to first event. The analysis population included all randomized participants who took at least one dose of blinded trial medication.

End point type	Primary
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End point timeframe:

Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants/100 Person-years				
number (not applicable)	2.96	2.97		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
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Statistical analysis description:

Based on the proportional hazards model that includes treatment as an explanatory factor.

Comparison groups	Omarigliptin 25 mg v Placebo
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Number of subjects included in analysis	4192
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.29

Primary: Change from Baseline in Hemoglobin A1C (A1C) at Week 18

End point title	Change from Baseline in Hemoglobin A1C (A1C) at Week 18
End point description:	
A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). This change from baseline reflects the Week 18 A1C minus the Week 0 A1C. The analysis population consisted of all randomized participants who received at least one dose of blinded study medication and had a baseline or a post-randomization measurement.	
End point type	Primary
End point timeframe:	
Baseline and Week 18	

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Percent				
least squares mean (confidence interval 95%)	-0.58 (-0.62 to -0.55)	-0.16 (-0.19 to -0.12)		

Statistical analyses

Statistical analysis title	Difference in the least squares means
Comparison groups	Omarigliptin 25 mg v Placebo
Number of subjects included in analysis	4192
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in the least squares means
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	-0.37

Primary: Change from Baseline in A1C at Week 18 in a Sub-Study of Participants Taking Insulin (With or Without Metformin)

End point title	Change from Baseline in A1C at Week 18 in a Sub-Study of Participants Taking Insulin (With or Without Metformin)
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End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). This change from baseline reflects the Week 18 A1C minus the Week 0 A1C. The analysis population consists of all randomized participants in a sub-study of participants taking insulin who received at least one dose of blinded study medication and had a baseline or a post-randomization measurement.

End point type	Primary
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End point timeframe:

Baseline and Week 18

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	535	509		
Units: Percentage				
least squares mean (confidence interval 95%)	-0.50 (-0.57 to -0.42)	-0.11 (-0.19 to -0.03)		

Statistical analyses

Statistical analysis title	Difference in the LS Means vs Placebo
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Statistical analysis description:

Longitudinal data analysis model including terms for treatment, time and the interaction of time by treatment.

Comparison groups	Omarigliptin 25 mg v Placebo
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Number of subjects included in analysis	1044
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Analysis specification	Pre-specified
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Analysis type	
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P-value	< 0.001
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Method	Longitudinal data analysis
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Parameter estimate	Difference in the LS Means vs Placebo
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Point estimate	-0.39
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Confidence interval	
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level	95 %
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sides	2-sided
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lower limit	-0.5
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upper limit	-0.27
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Primary: Percentage of Participants Who Experienced at Least One Adverse Event in

a Sub-study of Participants Taking Insulin Excluding Data After Background Antihyperglycemic Agent (AHA) Change

End point title	Percentage of Participants Who Experienced at Least One Adverse Event in a Sub-study of Participants Taking Insulin Excluding Data After Background Antihyperglycemic Agent (AHA) Change
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End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population included all randomized participants in a sub-study of participants taking insulin who received at least one dose of blinded study medication.

End point type	Primary
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End point timeframe:

Up to Week 18

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	535	509		
Units: Percentage of participants				
number (not applicable)	48.8	49.9		

Statistical analyses

Statistical analysis title	Difference in Percent vs. Placebo
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Statistical analysis description:

Based on Miettinen & Nurminen method. The 95% CI was computed only for those endpoints with at least 4 participants having events in one or more treatment groups.

Comparison groups	Omarigliptin 25 mg v Placebo
Number of subjects included in analysis	1044
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percent vs. Placebo
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	4.9

Primary: Percentage of Participants Who Discontinued from Study Drug Due to an Adverse Event in a Sub-Study of Participants Taking Insulin Excluding Data After Background AHA Change

End point title	Percentage of Participants Who Discontinued from Study Drug Due to an Adverse Event in a Sub-Study of Participants Taking Insulin Excluding Data After Background AHA Change
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End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population included all randomized participants in a sub-study of participants taking insulin who received at least one dose of blinded study medication.

End point type | Primary

End point timeframe:

Up to Week 18

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	535	509		
Units: Percentage of participants				
number (not applicable)	1.1	0.8		

Statistical analyses

Statistical analysis title | Difference in Percentage vs. Placebo

Statistical analysis description:

Based on Miettinen & Nurminen method. The 95% CI was computed only for those endpoints with at least 4 participants having events in one or more treatment groups.

Comparison groups | Omarigliptin 25 mg v Placebo

Number of subjects included in analysis | 1044

Analysis specification | Pre-specified

Analysis type

Parameter estimate | Difference in Percentage vs. Placebo

Point estimate | 0.3

Confidence interval

level | 95 %

sides | 2-sided

lower limit | -1

upper limit | 1.7

Secondary: Number of Participants with an Event of CV-Related Death

End point title | Number of Participants with an Event of CV-Related Death

End point description:

Participants with adjudicated and confirmed AEs of cardiovascular-related death. The analysis population consisted of all randomized participants who received at least one dose of blinded study medication.

End point type | Secondary

End point timeframe:

Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants	37	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event Per 100 Person-Years of CV-Related Death

End point title	Number of Participants with an Event Per 100 Person-Years of CV-Related Death
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End point description:

Participants with adjudicated and confirmed AEs of cardiovascular-related death. Person-years were calculated as the sum of all participants' follow-up time to event. The analysis population consisted of all participants who took at least one dose of blinded study medication.

End point type	Secondary
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End point timeframe:

Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants/100 person-years number (not applicable)	0.94	0.89		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
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Statistical analysis description:

Based on the proportional hazards model that includes treatment as an explanatory factor.

Comparison groups	Omarigliptin 25 mg v Placebo
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Number of subjects included in analysis	4192
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Analysis specification	Pre-specified
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Analysis type

Parameter estimate	Hazard ratio (HR)
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Point estimate	1.06
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Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.68

Secondary: Number of Participants With an Event of First MI (Fatal and Non-fatal)

End point title	Number of Participants With an Event of First MI (Fatal and Non-fatal)
End point description:	Participants with adjudicated and confirmed AEs of fatal and non-fatal MI. The analysis population consisted of all participants who took at least one dose of blinded study medication.
End point type	Secondary
End point timeframe:	Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants	52	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event Per 100 Person-Years of First MI (Fatal and Non-fatal)

End point title	Number of Participants with an Event Per 100 Person-Years of First MI (Fatal and Non-fatal)
End point description:	Participants with adjudicated and confirmed AEs of fatal and non-fatal MI. Person-years were calculated as the sum of all participants' follow-up time to first event. The analysis population consisted of all participants who took at least one dose of blinded study medication.
End point type	Secondary
End point timeframe:	Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants/100 person-years				
number (not applicable)	1.34	1.55		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Statistical analysis description: Based on the proportional hazards model that includes treatment as an explanatory factor.	
Comparison groups	Omarigliptin 25 mg v Placebo
Number of subjects included in analysis	4192
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.26

Secondary: Number of Participants With an Event of Stroke (Fatal and Non-fatal)

End point title	Number of Participants With an Event of Stroke (Fatal and Non-fatal)
End point description: Participants with adjudicated and confirmed AEs fatal and non-fatal stroke. The analysis population consisted of all participants who took at least one dose of blinded study medication.	
End point type	Secondary
End point timeframe: Up to 179 weeks	

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants	32	34		

Statistical analyses

Secondary: Number of Participants with an Event Per 100 Person-Years of First Stroke (Fatal and Non-fatal)

End point title	Number of Participants with an Event Per 100 Person-Years of First Stroke (Fatal and Non-fatal)
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End point description:

Participants with adjudicated and confirmed AEs fatal and non-fatal stroke. Person-years were calculated as the sum of all participants' follow-up time to event. The analysis population consisted of all participants who took at least one dose of blinded study medication.

End point type	Secondary
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End point timeframe:

Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants/100 person-years				
number (not applicable)	0.82	0.88		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
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Statistical analysis description:

Based on the proportional hazards model that includes treatment as an explanatory factor.

Comparison groups	Omarigliptin 25 mg v Placebo
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Number of subjects included in analysis	4192
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Analysis specification	Pre-specified
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Analysis type	
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Parameter estimate	Hazard ratio (HR)
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Point estimate	0.94
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.58
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upper limit	1.52
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Secondary: Number of Participants With an Event of All-Cause Death

End point title	Number of Participants With an Event of All-Cause Death
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End point description:

All-cause death was death from any cause. The analysis population included all randomized participants who took at least one dose of blinded trial medication.

End point type	Secondary
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End point timeframe:

Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants	64	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event Per 100 Person-Years of the Event of All-Cause Death

End point title	Number of Participants with an Event Per 100 Person-Years of the Event of All-Cause Death
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End point description:

All-cause death was death for any cause. Person-years were calculated as the sum of all participants' follow-up time to event. The analysis population included all randomized participants who took at least one dose of blinded study medication.

End point type	Secondary
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End point timeframe:

Up to 179 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants/100 Person-years				
number (not applicable)	1.63	1.28		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
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Statistical analysis description:

Based on the proportional hazards model that includes treatment as an explanatory factor.

Comparison groups	Omarigliptin 25 mg v Placebo
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Number of subjects included in analysis	4192
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.85

Secondary: Change from Baseline in A1C at Week 142

End point title	Change from Baseline in A1C at Week 142
End point description:	A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). This change from baseline reflects the Week 142 A1C minus the Week 0 A1C. The analysis population consisted of all randomized participants who received at least one dose of blinded study medication and had a baseline or a post-randomization measurement.
End point type	Secondary
End point timeframe:	Baseline and Week 142

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Percent				
least squares mean (confidence interval 95%)	-0.36 (-0.47 to -0.25)	-0.06 (-0.17 to 0.05)		

Statistical analyses

Statistical analysis title	Difference in the Least Squares Means
Statistical analysis description:	Longitudinal Data Analysis (LDA) model including terms for treatment, time, and the interaction of time by treatment.
Comparison groups	Omarigliptin 25 mg v Placebo
Number of subjects included in analysis	4192
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in the Least Squares Means
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.14

Secondary: Percentage of Participants Achieving a Target A1C <7.0 % (53 mmol/mol) at 4 Months

End point title	Percentage of Participants Achieving a Target A1C <7.0 % (53 mmol/mol) at 4 Months
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End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). Data for this efficacy endpoint was not collected, analyzed or summarized.

End point type	Secondary
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End point timeframe:

4 months

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[3] - Data for this efficacy endpoint was not collected, analyzed or summarized.

[4] - Data for this efficacy endpoint was not collected, analyzed or summarized.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at 4 months

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at 4 months
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End point description:

This change from baseline reflects the Month 4 FPG minus the Week 0 FPG. Data for this efficacy endpoint was not collected, analyzed or summarized.

End point type	Secondary
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End point timeframe:

Baseline and 4 months

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[5]	0 ^[6]		
Units: mg/dL				
least squares mean (confidence interval 95%)	(to)	(to)		

Notes:

[5] - Data for this efficacy endpoint was not collected, analyzed or summarized.

[6] - Data for this efficacy endpoint was not collected, analyzed or summarized.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initiation of Long-Term Insulin Therapy in Participants Not Receiving Insulin at Baseline

End point title	Time to Initiation of Long-Term Insulin Therapy in Participants Not Receiving Insulin at Baseline			
End point description:	Long-term insulin therapy was defined as a continuous period of insulin use of more than 3 months. Data for this efficacy endpoint was not collected, analyzed or summarized.			
End point type	Secondary			
End point timeframe:	Up to 179 weeks			

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: Weeks				
number (not applicable)				

Notes:

[7] - Data for this efficacy endpoint was not collected, analyzed or summarized.

[8] - Data for this efficacy endpoint was not collected, analyzed or summarized.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced at Least One Adverse Event

End point title	Percentage of Participants Who Experienced at Least One Adverse Event			
End point description:	An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population included all randomized participants who took at least one dose of blinded study medication.			
End point type	Secondary			
End point timeframe:	Up to 234 weeks			

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Percentage of participants				
number (not applicable)	78.3	76.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Discontinued from Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Discontinued from Study Drug Due to an Adverse Event
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End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population included all randomized participants who took at least one dose of blinded study medication.

End point type	Secondary
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End point timeframe:

Up to 212 weeks

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Percentage of participants				
number (not applicable)	4.1	3.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FPG at Week 18 in a Sub-Study of Participants Taking Insulin

End point title	Change from Baseline in FPG at Week 18 in a Sub-Study of Participants Taking Insulin
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End point description:

This change from baseline reflects the Week 18 FPG minus the Week 0 FPG. The analysis population consisted of all randomized participants in a sub-study of participants taking insulin who received at

least one dose of blinded study medication and had a baseline or a post-randomization measurement.

End point type	Secondary
End point timeframe:	
Baseline and Week 18	

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	535	509		
Units: mg/dL				
least squares mean (confidence interval 95%)	-6.8 (-12.1 to -1.5)	-3.6 (-9.1 to 1.8)		

Statistical analyses

Statistical analysis title	Difference in the least squares means
Statistical analysis description:	
Based on a LDA model including terms for treatment, time and the interaction of time by treatment.	
Comparison groups	Omarigliptin 25 mg v Placebo
Number of subjects included in analysis	1044
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.421
Method	Longitudinal constrained data analysis
Parameter estimate	Difference in the least squares means
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	4.5

Secondary: Percentage of Participants Achieving a Target A1C <7.0 % (53 mmol/mol) at Week 18 in a Sub-Study of Participants Taking Insulin

End point title	Percentage of Participants Achieving a Target A1C <7.0 % (53 mmol/mol) at Week 18 in a Sub-Study of Participants Taking Insulin
End point description:	
A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). Analysis was performed with multiple data imputation. The analysis population consisted of all randomized participants in a sub-study of participants taking insulin who received at least one dose of blinded study medication.	
End point type	Secondary
End point timeframe:	
18 weeks	

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	535	509		
Units: Percentage of participants				
number (confidence interval 95%)	22.0 (18.5 to 26.1)	10.2 (7.5 to 13.6)		

Statistical analyses

Statistical analysis title	Between group rate difference
Statistical analysis description:	
Estimated using standard multiple imputation techniques.	
Comparison groups	Omarigliptin 25 mg v Placebo
Number of subjects included in analysis	1044
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [9]
Method	Miettinen & Nurminen method
Parameter estimate	Between group rate difference
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	16.8

Notes:

[9] - Estimated using standard multiple imputation techniques.

Other pre-specified: Number of Participants With an Event of First Hospitalization for Heart Failure (Exploratory)

End point title	Number of Participants With an Event of First Hospitalization for Heart Failure (Exploratory)
End point description:	
Participants with adjudicated and confirmed events of first hospitalization for heart failure. The analysis population consisted of all participants who took at least one dose of blinded study medication.	
End point type	Other pre-specified
End point timeframe:	
Up to 179 weeks	

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants	20	33		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants with an Event Per 100 Person-years of the Event of the First Hospitalization for Heart Failure (Exploratory)

End point title	Number of Participants with an Event Per 100 Person-years of the Event of the First Hospitalization for Heart Failure (Exploratory)			
End point description:	Participants with adjudicated and confirmed events of first hospitalization for heart failure. Person-years were calculated as the sum of all participants' follow-up time to event. The analysis population consisted of all participants who took at least one dose of blinded study medication.			
End point type	Other pre-specified			
End point timeframe:	Up to 179 weeks			

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2092	2100		
Units: Participants/100 Person-years				
number (not applicable)	0.51	0.85		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)			
Statistical analysis description:	Based on the proportional hazards model that includes treatment as an explanatory factor.			
Comparison groups	Omarigliptin 25 mg v Placebo			
Number of subjects included in analysis	4192			
Analysis specification	Pre-specified			
Analysis type				
Parameter estimate	Hazard ratio (HR)			
Point estimate	0.6			

Confidence interval

level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 234 weeks

Adverse event reporting additional description:

Participants with serious adverse events with an incidence > 0% and with >5% non-serious adverse events in one or more treatment groups during the Treatment Period + Post-Treatment Follow-up including Post-21 days after last dose of blinded study treatment for randomized participants receiving one or more doses of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Omarigliptin 25 mg
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Reporting group description:

Omarigliptin (MK-3102) 25 mg capsule or tablet administered orally once weekly

Reporting group title	Placebo
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Reporting group description:

Matching placebo to omarigliptin capsule or tablet administered once weekly.

Serious adverse events	Omarigliptin 25 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	512 / 2092 (24.47%)	503 / 2100 (23.95%)	
number of deaths (all causes)	65	50	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	5 / 2092 (0.24%)	10 / 2100 (0.48%)	
occurrences causally related to treatment / all	0 / 6	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of eyelid			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	5 / 2100 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bone cancer		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Brain neoplasm		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer in situ		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer metastatic		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchial carcinoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Cholangiocarcinoma alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Colon adenoma alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Colon cancer alternative dictionary used: MedDRA 19.0 subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 3	0 / 1		
deaths causally related to treatment / all	0 / 1	0 / 0		
Colorectal cancer alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastric cancer alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 1	0 / 0		
Gastroesophageal cancer alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatic cancer alternative dictionary used: MedDRA 19.0				

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Lung carcinoma cell type unspecified stage IV			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Lung neoplasm malignant		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0
Lung squamous cell carcinoma stage II		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Malignant melanoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Meningioma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases to liver		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Metastatic gastric cancer		
alternative dictionary used: MedDRA 19.0		

subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Neoplasm malignant		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Neuroendocrine carcinoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Non-Hodgkin's lymphoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Oesophageal carcinoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic carcinoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	1 / 3	1 / 1
deaths causally related to treatment / all	1 / 3	1 / 1
Pancreatic carcinoma metastatic		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Pancreatic neoplasm alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	7 / 2092 (0.33%)	4 / 2100 (0.19%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer stage 0 alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer stage II alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal cancer		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cancer		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	4 / 2092 (0.19%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Renal cell carcinoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Small cell lung cancer		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Small cell lung cancer metastatic		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	5 / 2100 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0

Squamous cell carcinoma of skin alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer metastatic alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract neoplasm alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord neoplasm alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign ear neoplasm alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear neoplasm			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	2 / 2092 (0.10%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Dry gangrene		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Extremity necrosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Haematoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertension		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	7 / 2092 (0.33%)	8 / 2100 (0.38%)
occurrences causally related to treatment / all	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive crisis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive emergency		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Hypotension alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	14 / 2092 (0.67%)	10 / 2100 (0.48%)	
occurrences causally related to treatment / all	0 / 17	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	3 / 2092 (0.14%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	4 / 2100 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	4 / 2092 (0.19%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac death alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	6 / 2092 (0.29%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Death		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	4 / 2092 (0.19%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 0
Multiple organ dysfunction syndrome		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 1
Non-cardiac chest pain		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	8 / 2100 (0.38%)
occurrences causally related to treatment / all	0 / 5	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Sudden cardiac death		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	4 / 2100 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 4
Sudden death		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	6 / 2092 (0.29%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 6	0 / 3
Vascular stent restenosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Catheter site haemorrhage alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent thrombosis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders Drug hypersensitivity alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders Benign prostatic hyperplasia alternative dictionary used: MedDRA 19.0 subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast fibrosis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital prolapse			

alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic dysplasia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	2 / 2092 (0.10%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	6 / 2092 (0.29%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	7 / 2092 (0.33%)	5 / 2100 (0.24%)	
occurrences causally related to treatment / all	0 / 9	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	5 / 2100 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural effusion		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pleurisy		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia aspiration		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumothorax		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary embolism		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0

Pulmonary mass alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema alternative dictionary used: MedDRA 19.0 subjects affected / exposed	3 / 2092 (0.14%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure alternative dictionary used: MedDRA 19.0 subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sleep apnoea syndrome alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders Abnormal behaviour alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute stress disorder alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Somatic symptom disorder alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced mood disorder alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues Device breakage alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations Blood creatinine increased alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	6 / 2100 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium decreased alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate increased alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications Acetabulum fracture alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ankle fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Avulsion fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac procedure complication		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cervical vertebral fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chemical peritonitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Concussion		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Contusion alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery restenosis alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Femur fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Fibula fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Flail chest		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Foot fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Forearm fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal anastomotic leak		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Head injury alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated incisional hernia alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Limb injury		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower limb fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Meniscus injury		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Multiple injuries		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural complication		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Post procedural haemorrhage		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Postoperative ileus alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Soft tissue injury alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury cervical alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Stomal hernia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Subdural haematoma		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Synovial rupture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thermal burn		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tibia fracture		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Toxicity to various agents		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Traumatic haemorrhage alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Upper limb fracture alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vascular graft occlusion alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vascular pseudoaneurysm alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Wrist fracture alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Procedural pneumothorax alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Traumatic intracranial haemorrhage alternative dictionary used: MedDRA 19.0				

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital claw toe			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalocele			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	3 / 2092 (0.14%)	7 / 2100 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	30 / 2092 (1.43%)	27 / 2100 (1.29%)	
occurrences causally related to treatment / all	2 / 35	0 / 28	
deaths causally related to treatment / all	0 / 5	0 / 2	
Angina pectoris			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	27 / 2092 (1.29%)	31 / 2100 (1.48%)	
occurrences causally related to treatment / all	0 / 29	0 / 36	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	33 / 2092 (1.58%)	42 / 2100 (2.00%)
occurrences causally related to treatment / all	0 / 39	0 / 46
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic valve stenosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriosclerosis coronary artery		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial fibrillation		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	14 / 2092 (0.67%)	16 / 2100 (0.76%)
occurrences causally related to treatment / all	0 / 14	0 / 17
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial flutter		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial tachycardia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Atrioventricular block complete alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	3 / 2092 (0.14%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac aneurysm alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	9 / 2092 (0.43%)	4 / 2100 (0.19%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 7	0 / 2	
Cardiac failure alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	17 / 2092 (0.81%)	12 / 2100 (0.57%)	
occurrences causally related to treatment / all	0 / 21	1 / 12	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiac failure acute alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	6 / 2092 (0.29%)	4 / 2100 (0.19%)
occurrences causally related to treatment / all	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 2
Cardiac failure chronic alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	7 / 2092 (0.33%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure congestive alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	14 / 2092 (0.67%)	20 / 2100 (0.95%)
occurrences causally related to treatment / all	0 / 16	1 / 25
deaths causally related to treatment / all	0 / 3	0 / 2
Cardio-respiratory arrest alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 3
Cardiogenic shock alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	4 / 2100 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 3
Cardiomyopathy alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiopulmonary failure alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	4 / 2100 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 3

Conduction disorder alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cor pulmonale alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coronary artery disease alternative dictionary used: MedDRA 19.0 subjects affected / exposed	22 / 2092 (1.05%)	23 / 2100 (1.10%)		
occurrences causally related to treatment / all	0 / 24	0 / 24		
deaths causally related to treatment / all	0 / 1	0 / 1		
Coronary artery insufficiency alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coronary artery occlusion alternative dictionary used: MedDRA 19.0 subjects affected / exposed	3 / 2092 (0.14%)	4 / 2100 (0.19%)		
occurrences causally related to treatment / all	0 / 3	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coronary artery stenosis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	9 / 2092 (0.43%)	6 / 2100 (0.29%)		
occurrences causally related to treatment / all	0 / 9	0 / 6		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ischaemic cardiomyopathy alternative dictionary used: MedDRA 19.0				

subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Left ventricular failure		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial infarction		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	19 / 2092 (0.91%)	17 / 2100 (0.81%)
occurrences causally related to treatment / all	0 / 19	0 / 19
deaths causally related to treatment / all	0 / 5	0 / 3
Myocardial ischaemia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1
Myocardial reperfusion injury		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pericardial effusion		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Right ventricular failure		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Silent myocardial infarction alternative dictionary used: MedDRA 19.0 subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sinus node dysfunction alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Supraventricular tachycardia alternative dictionary used: MedDRA 19.0 subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 4	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ventricular arrhythmia alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ventricular extrasystoles alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)		
occurrences causally related to treatment / all	0 / 1	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ventricular fibrillation alternative dictionary used: MedDRA 19.0 subjects affected / exposed	3 / 2092 (0.14%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Ventricular tachyarrhythmia alternative dictionary used: MedDRA 19.0				

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifascicular block alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia infarction alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia stroke alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	4 / 2092 (0.19%)	7 / 2100 (0.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	4 / 2092 (0.19%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ischaemia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebral small vessel ischaemic disease			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	9 / 2092 (0.43%)	9 / 2100 (0.43%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular insufficiency			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dementia			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dementia Alzheimer's type		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic neuropathy		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dizziness		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Embolic stroke		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Encephalopathy		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Epilepsy		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Facial paralysis alternative dictionary used: MedDRA 19.0				
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Haemorrhagic stroke alternative dictionary used: MedDRA 19.0				
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 1		
Headache alternative dictionary used: MedDRA 19.0				
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hypertensive encephalopathy alternative dictionary used: MedDRA 19.0				
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
IIIrd nerve paralysis alternative dictionary used: MedDRA 19.0				
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intracranial aneurysm alternative dictionary used: MedDRA 19.0				
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ischaemic stroke alternative dictionary used: MedDRA 19.0				

subjects affected / exposed	11 / 2092 (0.53%)	17 / 2100 (0.81%)
occurrences causally related to treatment / all	0 / 11	0 / 17
deaths causally related to treatment / all	0 / 0	0 / 1
Lacunar infarction		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Loss of consciousness		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar radiculopathy		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Meralgia paraesthetica		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Migraine		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Monoparesis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Myelitis transverse alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	7 / 2092 (0.33%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Toxic encephalopathy		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Transient ischaemic attack		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	11 / 2092 (0.53%)	11 / 2100 (0.52%)
occurrences causally related to treatment / all	0 / 11	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0
Vlith nerve paralysis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular dementia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vertebrobasilar insufficiency		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebellar infarction		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Blood and lymphatic system disorders			
Agranulocytosis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	6 / 2092 (0.29%)	4 / 2100 (0.19%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation factor deficiency			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytosis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness unilateral			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acquired oesophageal web			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal spasm			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroenteropathy			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer haemorrhage		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric varices haemorrhage		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis erosive		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroduodenitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Gastrointestinal disorder alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Incarcerated umbilical hernia alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Inguinal hernia alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal obstruction alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Large intestine polyp alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	4 / 2100 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Lower gastrointestinal haemorrhage alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Noninfective gingivitis alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Oesophagitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	3 / 2092 (0.14%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated umbilical hernia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholangitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	7 / 2092 (0.33%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis acute		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	4 / 2092 (0.19%)	4 / 2100 (0.19%)
occurrences causally related to treatment / all	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis chronic		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cholelithiasis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic cirrhosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Hepatorenal syndrome alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatosis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	6 / 2092 (0.29%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	11 / 2092 (0.53%)	6 / 2100 (0.29%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Calculus urethral			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dysuria		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haematuria		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhage urinary tract		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nephrolithiasis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Renal colic		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal failure		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Stag horn calculus alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders Goitre alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Amyotrophy			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gouty arthritis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc disorder		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc protrusion		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	4 / 2100 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar spinal stenosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscular weakness		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Osteitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	14 / 2092 (0.67%)	9 / 2100 (0.43%)	
occurrences causally related to treatment / all	0 / 15	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	4 / 2092 (0.19%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Appendicitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Atypical pneumonia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial sepsis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	6 / 2092 (0.29%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis viral		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchopulmonary aspergillosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Bronchopulmonary aspergillosis allergic			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	11 / 2092 (0.53%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 11	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic hepatitis C			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Endocarditis bacterial		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Endophthalmitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enterococcal sepsis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Epididymitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Erysipelas		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia urinary tract infection		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0

Febrile infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	6 / 2092 (0.29%)	4 / 2100 (0.19%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gas gangrene			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	3 / 2092 (0.14%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIV infection			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Mediastinitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neuroborreliosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nosocomial infection		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Paronychia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic sepsis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	35 / 2092 (1.67%)	31 / 2100 (1.48%)	
occurrences causally related to treatment / all	0 / 37	0 / 31	
deaths causally related to treatment / all	0 / 4	0 / 2	
Pneumonia respiratory syncytial viral			
alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia streptococcal		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia viral		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative abscess		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary tuberculosis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis acute		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Respiratory tract infection alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	2 / 2092 (0.10%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	7 / 2092 (0.33%)	5 / 2100 (0.24%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Septic shock alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sinusitis alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural empyema alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	4 / 2092 (0.19%)	6 / 2100 (0.29%)
occurrences causally related to treatment / all	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection bacterial alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urosepsis alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Viral infection alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	2 / 2092 (0.10%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vulval abscess alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Wound infection alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	2 / 2100 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus alternative dictionary used: MedDRA 19.0 subjects affected / exposed	1 / 2092 (0.05%)	3 / 2100 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control alternative dictionary used: MedDRA 19.0 subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis alternative dictionary used: MedDRA 19.0 subjects affected / exposed	3 / 2092 (0.14%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation alternative dictionary used: MedDRA 19.0			

subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fluid overload		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gout		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	1 / 2092 (0.05%)	0 / 2100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	5 / 2092 (0.24%)	7 / 2100 (0.33%)
occurrences causally related to treatment / all	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperkalaemia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoglycaemia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	3 / 2092 (0.14%)	5 / 2100 (0.24%)
occurrences causally related to treatment / all	2 / 4	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Hypokalaemia		
alternative dictionary used: MedDRA 19.0		
subjects affected / exposed	0 / 2092 (0.00%)	1 / 2100 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Obesity			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 2092 (0.05%)	1 / 2100 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Omarigliptin 25 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	788 / 2092 (37.67%)	794 / 2100 (37.81%)	
Investigations			
Blood glucose increased			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	97 / 2092 (4.64%)	139 / 2100 (6.62%)	
occurrences (all)	139	199	
Infections and infestations			
Nasopharyngitis			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	123 / 2092 (5.88%)	145 / 2100 (6.90%)	
occurrences (all)	167	195	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	123 / 2092 (5.88%)	120 / 2100 (5.71%)	
occurrences (all)	163	150	
Urinary tract infection			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	108 / 2092 (5.16%)	98 / 2100 (4.67%)	
occurrences (all)	131	141	
Metabolism and nutrition disorders			
Hypoglycaemia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	530 / 2092 (25.33%)	473 / 2100 (22.52%)	
occurrences (all)	3990	3688	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2012	Amendment 1: The primary reason for this amendment was inclusion of a trial design figure.
22 January 2013	Amendment 2: The primary reason for this amendment was a modified inclusion criteria and contraception language as results were available from the Phase I trial on drug-drug interaction with oral contraceptives.
05 March 2013	Amendment 5: Clarified the insulin use allowed in an inclusion criterion.
26 February 2014	Amendment 3: In order to comply with regulatory guidance in Brazil, the Future Biomedical Research information and procedures in the protocol were removed and were presented in a stand-alone protocol amendment.
26 February 2014	Amendment 4: In order to comply with regulatory guidance in Brazil, the Future Biomedical Research information were presented in a stand-alone protocol amendment
13 May 2014	<p>Amendment 6:</p> <ul style="list-style-type: none"> • Addition of an insulin sub-study in the sub-population of participants receiving background insulin with or without metformin. • Change in the A1C inclusion criterion to 6.5%-10.0% for potential trial participants who are not on monotherapy or dual combination therapy with sulfonylureas, meglitinides or insulin. • Change in enrollment criteria to allow enrollment of participants on prandial insulin. • Provide guidance on the rescreening of potential trial participants secondary the changes in inclusion and exclusion criteria in the current amendment. • Removal of metformin-specific serum creatinine and estimated glomerular filtration rate (eGFR) exclusion criteria. • Change in the eGFR exclusion from $<30 \text{ mL/min/1.73 m}^2$ to $<40 \text{ mL/min/1.73 m}^2$ to provide a "window" between the Visit 1 exclusion criterion and the discontinuation criterion of $<30 \text{ mL/min/1.73 m}^2$. • Exclusion of potential cardiovascular endpoints from expedited serious adverse event (SAE) reporting.
03 November 2015	<p>Amendment 7</p> <ul style="list-style-type: none"> •The primary change is to extend the length of the trial. •Text is incorporated to allow additional participants (Cohort 2) to be enrolled if required. •Objectives and hypothesis relevant to meeting the United States Food and Drug Administration (US FDA) requirements for the post-approval assessment of cardiovascular (CV) safety were added. •Terminology has been introduced which refers to the stages of the CV safety assessment (Stage 1 and Stage 2), trial data collection periods (Period 1 and Period 2), and participant cohorts (Cohort 1 and Cohort 2). •Updated Power and Sample Size in addition to the Statistical Analysis sections to reflect the US FDA post-approval CV safety requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported