Clinical trial results:
A Double Blind, Randomized, Placebo Controlled, Parallel Group Study to Simultaneously Qualify a Biomarker Algorithm for Prognosis of Risk of Developing Mild Cognitive Impairment due to Alzheimer's Disease (MCI due to AD) and to Test the Safety and Efficacy of Pioglitazone (AD-4833 SR 0.8 mg QD) to Delay the Onset of MCI due to AD in Cognitively Normal Subjects

Summary

EudraCT number	2012-003111-58
Trial protocol	GB IT DE
Global end of trial date	06 September 2018

Results information

Result version number	v1 (current)
This version publication date	07 August 2019
First version publication date	07 August 2019

Trial information

Trial identification

Sponsor protocol code	AD-4833/TOMM40_301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01931566
WHO universal trial number (UTN)	U1111-1139-0355

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	One Takeda Parkway, Deerfield, IL, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda Development Center Americas, Inc., +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Clinical Science, Takeda Development Center Americas, Inc., +1 877-825-3327, clinicaltrialregistry@tpna.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	06 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to qualify the biomarker risk algorithm composed of TOMM40 rs10524523 genotype, apolipoprotein E (APOE) genotype, and age for prognosis of the risk of developing mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) within 5 years; and to evaluate the efficacy of pioglitazone compared with placebo to delay the onset of MCI due to AD in cognitively-normal subjects who are at high-risk, as identified by the biomarker risk algorithm at enrollment, for developing MCI due to AD within 5 years.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 489
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Switzerland: 39
Country: Number of subjects enrolled	United Kingdom: 728
Country: Number of subjects enrolled	United States: 2217
Worldwide total number of subjects	3494
EEA total number of subjects	749

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)	0
From 65 to 84 years	3494
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 57 investigative sites in United States, United Kingdom, Germany, Australia, and Switzerland from 01 Aug 2013 to 06 Sep 2018.

Pre-assignment

Screening details:

Participants with a diagnosis of MCI due to AD were enrolled to receive either pioglitazone (0.8 mg sustained release tablet) or placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Low Risk Placebo

Arm description:

Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to low risk group for developing MCI-AD for up to 5 years.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pioglitazone placebo-matching tablets

Arm title	High Risk Placebo

Arm description:

Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pioglitazone placebo-matching tablets

Arm title	High Risk Pioglitazone

Arm description:

Pioglitazone 0.8 mg, sustained release (SR) tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.

Arm type	Experimental

Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	AD-4833
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pioglitazone tablets

Number of subjects in period 1	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Started	433	1516	1545
Treated	423	1467	1491
Completed	4	40	39
Not completed	429	1476	1506
Major Protocol Deviation	5	14	21
Study Termination	289	968	1037
Adverse event, non-fatal	37	167	132
Voluntary Withdrawal	78	245	225
Reason Not Specified	11	47	53
Randomized But Not Treated	6	9	14
Lost to follow-up	3	26	23
Missing	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Low Risk Placebo
Reporting group description:	
Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to low risk group for developing MCI-AD for up to 5 years.	
Reporting group title	High Risk Placebo
Reporting group description:	
Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.	
Reporting group title	High Risk Pioglitazone
Reporting group description:	
Pioglitazone 0.8 mg, sustained release (SR) tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.	

Reporting group values	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Number of subjects	433	1516	1545
Age, Customized Units: Subjects			
<75 years	360	632	658
>=75 years	73	884	887
Age Continuous Units: years			
arithmetic mean	70.3	74.6	74.4
standard deviation	± 4.02	± 5.27	± 5.25
Sex: Female, Male Units: Subjects			
Female	259	850	812
Male	174	666	733
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8	19	12
Not Hispanic or Latino	425	1497	1533
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	4
Asian	1	10	14
Black or African American	10	38	39
Native Hawaiian or Other Pacific Islander	0	1	1
White	421	1463	1484
Multiracial	1	4	3
Race/Ethnicity, Customized Units: Subjects			
Non-Hispanic/Latino Caucasian	413	1444	1472
Hispanic/Latino and/or non-Caucasian	20	72	73
Region of Enrollment			

Units: Subjects			
United States|	270	962	985
United Kingdom|	102	311	315
Australia|	56	215	218
Switzerland|	3	18	18
Germany|	2	10	9

Reporting group values	Total		
Number of subjects	3494		
Age, Customized Units: Subjects			
<75 years	1650		
>=75 years	1844		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	1921		
Male	1573		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	39		
Not Hispanic or Latino	3455		
Unknown or Not Reported	0		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	4		
Asian	25		
Black or African American	87		
Native Hawaiian or Other Pacific Islander	2		
White	3368		
Multiracial	8		
Race/Ethnicity, Customized Units: Subjects			
Non-Hispanic/Latino Caucasian	3329		
Hispanic/Latino and/or non-Caucasian	165		
Region of Enrollment Units: Subjects			
United States|	2217		
United Kingdom|	728		
Australia|	489		
Switzerland|	39		
Germany|	21		

End points

End points reporting groups

Reporting group title	Low Risk Placebo
Reporting group description:	
Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to low risk group for developing MCI-AD for up to 5 years.	
Reporting group title	High Risk Placebo
Reporting group description:	
Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.	
Reporting group title	High Risk Pioglitazone
Reporting group description:	
Pioglitazone 0.8 mg, sustained release (SR) tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.	

Primary: Time to Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease (MCI-AD) for Placebo-treated, High-risk, Non-Hispanic/Latino Caucasian Participants versus Placebo-treated, Low-risk, Non-Hispanic/Latino Caucasian Participants

End point title	Time to Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease (MCI-AD) for Placebo-treated, High-risk, Non-Hispanic/Latino Caucasian Participants versus Placebo-treated, Low-risk, Non-Hispanic/Latino Caucasian Participants[1]
End point description:	
The event definition for MCI-AD was the time in days from the randomization date to the date of the first of two consecutive scheduled visits at which a participant was assessed with a diagnosis of MCI due to AD confirmed by adjudication committee. Here, the time to event was reported as the restricted mean survival time. The restricted mean survival time was defined as the area under the curve of the survival function up to the largest event time. Full Analysis Set (FAS) included all participants who were randomized, received at least 1 dose of study drug, and at least 1 valid postbaseline value for assessment of primary efficacy. A participant who did not have an event of MCI due to AD was censored at the date of the last visit at which MCI due to AD could have been assessed.	
End point type	Primary
End point timeframe:	
Baseline to the end of study (approximately up to 5 years)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned in the participants who received a placebo.

End point values	Low Risk Placebo	High Risk Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	1406		
Units: days				
arithmetic mean (full range (min-max))	905.44 (189.00 to 909.00)	1238.67 (168.00 to 1268.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Low Risk Placebo v High Risk Placebo
Number of subjects included in analysis	1808
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.016 [2]
Method	Weighted Generalized Log Rank Test

Notes:

[2] - P-value comparing high risk to low risk placebo was obtained using weighted generalized log-rank test stratified by gender as nonparametric analysis.

Primary: Time to Diagnosis of MCI due to AD for Pioglitazone-treated, High-risk, Non-Hispanic/Latino Caucasian Participants versus Placebo-treated, High-risk, Non-Hispanic/Latino, Caucasian Participants

End point title	Time to Diagnosis of MCI due to AD for Pioglitazone-treated, High-risk, Non-Hispanic/Latino Caucasian Participants versus Placebo-treated, High-risk, Non-Hispanic/Latino, Caucasian Participants[3]

End point description:

The event definition for MCI-AD was the time in days from the randomization date to the date of the first of two consecutive scheduled visits at which a participant was assessed with a diagnosis of MCI due to AD confirmed by adjudication committee. Here, the time to event was reported as the restricted mean survival time. The restricted mean survival time was defined as the area under the curve of the survival function up to the largest event time. FAS included all participants who were randomized, received at least 1 dose of study drug, and at least 1 valid postbaseline value for assessment of primary efficacy. A participant who did not have an event of MCI due to AD was censored at the date of the last visit at which MCI due to AD could have been assessed.

End point type	Primary

End point timeframe:

Baseline to the end of study (approximately up to 5 years)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned in the High-risk stratum of participants.

End point values	High Risk Placebo	High Risk Pioglitazone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1406	1430		
Units: days				
arithmetic mean (full range (min-max))	1238.67 (168.00 to 1268.00)	1261.24 (168.00 to 1285.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	High Risk Placebo v High Risk Pioglitazone

Number of subjects included in analysis	2836
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.314 [4]
Method	Weighted Generalized Log Rank Test

Notes:

[4] - P-value comparing active to placebo was obtained using the weighted generalized log-rank test stratified by gender as a nonparametric analysis.

Secondary: Change from Baseline for Cognitive Decline on Composite Score on the Cognitive Test Battery for Pioglitazone-treated Participants versus Placebo-treated Participants in the High-risk Stratum

End point title	Change from Baseline for Cognitive Decline on Composite Score on the Cognitive Test Battery for Pioglitazone-treated Participants versus Placebo-treated Participants in the High-risk Stratum[5]

End point description:

Composite scores derived from the test battery. Domains of Episodic Memory [California Verbal Learning Test-2nd Edition (CVLT-II), Brief Visuospatial Memory Test-Revised (BVMT-R)]; Executive Function [Trail Making Test (TMT) (Part B), Wechsler Adult Intelligence Scale (WAIS)-III Digit Span Test-backwards span]; Language [Multilingual Naming Test (MiNT), Semantic Fluency (animals), Lexical/phonemic fluency (F, A, and S in English; D, S, and F in German)]; and Attention [WAIS-III Digit Span Test-forward span, TMT (Part A)] used for composite score. 12 measures were derived from 8 neuropsychological tests. CVLT-II test involved 2 primary measures (short, long delay recall); BVMT-R had 2 measures (copy and recall); Digit Span and Trail both had 2 measures (forward and backward span and Parts A and B). There was 1 total score for each test: CDT, MINT, semantic and lexical fluency. Total score ranged from -1.222 to 1.707 at baselinbe, a higher composite score indicated better cognition.

End point type	Secondary

End point timeframe:

Baseline and Months 6, 12, 18, 24, 30, 36, 42 and 48

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned in the High-risk stratum of participants.

End point values	High Risk Placebo	High Risk Pioglitazone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1406	1430		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Month 6|	0.0186 (± 0.30742)	0.0338 (± 0.29547)		
Change at Month 12|	0.0682 (± 0.30721)	0.0904 (± 0.29531)		
Change at Month 18|	0.0752 (± 0.31077)	0.0892 (± 0.30919)		
Change at Month 24|	0.1005 (± 0.31814)	0.1189 (± 0.30424)		
Change at Month 30|	0.1202 (± 0.33480)	0.1297 (± 0.31836)		
Change at Month 36|	0.1507 (± 0.32076)	0.1436 (± 0.31619)		
Change at Month 42|	0.1501 (± 0.32423)	0.0973 (± 0.32720)		
Change at Month 48|	0.1841 (± 0.27508)	0.1687 (± 0.40621)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Instrumental Activities of Daily Living (Alzheimer's Disease Cooperative Study Activities of Daily Living - Prevention Instrument [ADCS ADL-PI]) between Pioglitazone-treated and Placebo-treated Groups of the High-risk Stratum

End point title	Change from Baseline in Instrumental Activities of Daily Living (Alzheimer's Disease Cooperative Study Activities of Daily Living - Prevention Instrument [ADCS ADL-PI]) between Pioglitazone-treated and Placebo-treated Groups of the High-risk Stratum[6]

End point description:

The ADCS ADL-PI is a functional measure that was specifically designed for standardized administration over long duration clinical studies to prevent AD. The ADCS ADL-PI is a 20-item instrument that included 15 ADL questions, which were scored as 1 (with a lot of difficulty), 2 (with some difficulty), or 3 (as well as usually, with no difficulty), plus 5 vision, hearing, and mobility questions, which were scored from 0 (no) to 1 (yes). ADL Total ranged from 0 to 45, and lower scores indicated greater disability. Full Analysis Set (FAS) included all participants who were randomized, received at least 1 dose of study drug, and at least 1 valid postbaseline value for assessment of primary efficacy. A participant who does not have an event of MCI due to AD was censored at the date of the last visit at which MCI due to AD could have been assessed.

End point type	Secondary

End point timeframe:

Baseline and Months 6, 12, 18, 24, 30, 36, 42 and 48

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned in the High-risk stratum of participants.

End point values	High Risk Placebo	High Risk Pioglitazone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1406	1430		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Month 6|	0.1 (± 3.54)	0.1 (± 3.50)		
Change at Month 12|	0.0 (± 3.99)	0.1 (± 3.95)		
Change at Month 18|	0.1 (± 3.87)	0.2 (± 3.59)		
Change at Month 24|	0.3 (± 3.78)	0.2 (± 3.63)		
Change at Month 30|	0.3 (± 3.76)	0.1 (± 3.61)		
Change at Month 36|	0.2 (± 3.77)	0.2 (± 3.72)		
Change at Month 42|	0.3 (± 3.63)	0.3 (± 3.74)		
Change at Month 48|	0.1 (± 4.93)	0.3 (± 5.32)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last dose of study drug (up to 935 days)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Low Risk Placebo

Reporting group description:

Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to low risk group for developing MCI-AD for up to 5 years.

Reporting group title	High Risk Placebo

Reporting group description:

Pioglitazone placebo-matching tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.

Reporting group title	High Risk Pioglitazone

Reporting group description:

Pioglitazone 0.8 mg, sustained release (SR) tablets, orally, once daily to participants assigned to high risk group for developing MCI-AD for up to 5 years.

Serious adverse events	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 427 (18.97%)	404 / 1507 (26.81%)	358 / 1531 (23.38%)
number of deaths (all causes)	2	21	7
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 427 (0.23%)	8 / 1507 (0.53%)	5 / 1531 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	2 / 427 (0.47%)	2 / 1507 (0.13%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancreatic carcinoma	Additional description: One treatment-emergent death occurred during treatment with placebo (in low-risk group) and was not related. Two treatment-emergent deaths occurred during treatment with placebo (in high-risk group) and were not related.		
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 427 (0.23%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma pancreas			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	2 / 427 (0.47%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung	Additional description: One treatment-emergent death occurred during treatment with pioglitazone (in high-risk group) and was not related.		

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Anal squamous cell carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign renal neoplasm			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer stage 0, with cancer in situ			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer in situ			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac myxoma			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma	Additional description: One treatment-emergent death occurred during treatment with pioglitazone (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Choroid plexus papilloma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer stage II			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular thyroid cancer			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial meningioma malignant			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive papillary breast carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine benign neoplasm			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma stage II			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mantle cell lymphoma recurrent			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucinous breast carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer stage IIIB			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophageal carcinoma	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was related.		
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophageal squamous cell carcinoma			

subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasmacytoma	Additional description: One treatment-emergent death occurred during treatment with pioglitazone (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Polycythaemia vera			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schwannoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord neoplasm			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension	Additional description: One treatment-emergent death occurred during treatment with placebo (in low-risk group) and was not related.		
subjects affected / exposed	1 / 427 (0.23%)	4 / 1507 (0.27%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			

subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior mesenteric artery syndrome			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Shoulder arthroplasty			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 427 (0.00%)	5 / 1507 (0.33%)	8 / 1531 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adverse drug reaction			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ill-defined disorder			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unevaluable event			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcoidosis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 427 (0.47%)	4 / 1507 (0.27%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatomegaly			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal prolapse			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acquired hydrocele			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterovaginal prolapse			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vaginal haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 427 (0.23%)	9 / 1507 (0.60%)	11 / 1531 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 9	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	2 / 427 (0.47%)	6 / 1507 (0.40%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 427 (0.00%)	4 / 1507 (0.27%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 427 (0.23%)	2 / 1507 (0.13%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Asthma			
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure	Additional description: One treatment-emergent death occurred during treatment with pioglitazone (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough	Additional description: One treatment-emergent death occurred during treatment with pioglitazone (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Interstitial lung disease			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary granuloma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol abuse			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	6 / 1531 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 427 (0.47%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Primary biliary cholangitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood magnesium decreased			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood parathyroid hormone increased			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate irregular			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			

subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 427 (0.23%)	7 / 1507 (0.46%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	2 / 427 (0.47%)	7 / 1507 (0.46%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 427 (0.00%)	4 / 1507 (0.27%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage	Additional description: Two treatment-emergent deaths occurred during treatment with placebo (in high-risk group) and were not related.		
subjects affected / exposed	0 / 427 (0.00%)	4 / 1507 (0.27%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			

subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic osteolysis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Avulsion fracture			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation complication			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural haematoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flatback syndrome			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured ischium			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative respiratory failure			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural intestinal perforation			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural vomiting			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress fracture			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage	Additional description: One treatment-emergent death occurred in participant who also suffered from cerebrovascular accident during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tendon injury			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital cerebrovascular anomaly			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 427 (1.17%)	15 / 1507 (1.00%)	16 / 1531 (1.05%)
occurrences causally related to treatment / all	0 / 6	0 / 20	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina pectoris			
subjects affected / exposed	3 / 427 (0.70%)	10 / 1507 (0.66%)	6 / 1531 (0.39%)
occurrences causally related to treatment / all	0 / 4	0 / 10	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 427 (0.47%)	7 / 1507 (0.46%)	7 / 1531 (0.46%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction	Additional description: Four treatment-emergent deaths occurred during treatment with placebo (in high-risk group) and were not related.		
subjects affected / exposed	0 / 427 (0.00%)	13 / 1507 (0.86%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 13	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Cardiac failure congestive	Additional description: Two treatment-emergent deaths occurred during treatment with placebo (in high-risk group) and were not related.		
subjects affected / exposed	1 / 427 (0.23%)	8 / 1507 (0.53%)	6 / 1531 (0.39%)
occurrences causally related to treatment / all	1 / 1	1 / 11	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Acute myocardial infarction	Additional description: One treatment-emergent death occurred during treatment with pioglitazone (in high-risk group) and was not related.		
subjects affected / exposed	1 / 427 (0.23%)	5 / 1507 (0.33%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus node dysfunction			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	5 / 1531 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 427 (0.00%)	4 / 1507 (0.27%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	5 / 1531 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest	Additional description: Two treatment-emergent deaths occurred during		

	treatment with placebo (in high-risk group) and were not related.		
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 427 (0.23%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia	Additional description: One treatment-emergent death occurred during treatment with pioglitazone (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aortic valve stenosis			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrasystoles			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriospasm coronary			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial septal defect acquired			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve disease			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 427 (0.47%)	13 / 1507 (0.86%)	14 / 1531 (0.91%)
occurrences causally related to treatment / all	0 / 2	0 / 13	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 427 (0.00%)	11 / 1507 (0.73%)	10 / 1531 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 11	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident	Additional description: One treatment-emergent death occurred in participant who also suffered from subdural haemorrhage during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	1 / 427 (0.23%)	10 / 1507 (0.66%)	6 / 1531 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 10	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Presyncope			
subjects affected / exposed	1 / 427 (0.23%)	4 / 1507 (0.27%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was not related.		

subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Seizure			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amnesia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness postural			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial neuralgia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IIIrd nerve paralysis			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal lobe epilepsy			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Macular fibrosis			
subjects affected / exposed	2 / 427 (0.47%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cataract			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dacryostenosis acquired			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neovascular age-related macular degeneration			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 427 (0.00%)	8 / 1507 (0.53%)	5 / 1531 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	5 / 1531 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rectal haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal adhesions			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal stenosis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallstone ileus			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Precancerous skin lesion			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 427 (0.70%)	5 / 1507 (0.33%)	7 / 1531 (0.46%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			

subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic nephropathy			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower urinary tract symptoms			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	4 / 427 (0.94%)	22 / 1507 (1.46%)	23 / 1531 (1.50%)
occurrences causally related to treatment / all	0 / 6	0 / 24	0 / 26
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	3 / 427 (0.70%)	13 / 1507 (0.86%)	10 / 1531 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 14	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 427 (0.23%)	6 / 1507 (0.40%)	8 / 1531 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 427 (0.47%)	4 / 1507 (0.27%)	5 / 1531 (0.33%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc degeneration			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			

subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 427 (0.23%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dupuytren's contracture			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture pain			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint instability			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myosclerosis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in jaw			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sacroiliitis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scoliosis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seronegative arthritis			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon disorder			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral osteophyte			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia	Additional description: One treatment-emergent death occurred during treatment with placebo (in high-risk group) and was not related.		
subjects affected / exposed	3 / 427 (0.70%)	12 / 1507 (0.80%)	15 / 1531 (0.98%)
occurrences causally related to treatment / all	0 / 3	0 / 13	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diverticulitis			

subjects affected / exposed	3 / 427 (0.70%)	7 / 1507 (0.46%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	8 / 1531 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 427 (0.23%)	5 / 1507 (0.33%)	6 / 1531 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	2 / 427 (0.47%)	4 / 1507 (0.27%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 427 (0.23%)	5 / 1507 (0.33%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	2 / 427 (0.47%)	1 / 1507 (0.07%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 427 (0.00%)	3 / 1507 (0.20%)	4 / 1531 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 427 (0.23%)	2 / 1507 (0.13%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 427 (0.00%)	4 / 1507 (0.27%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	2 / 1531 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 427 (0.23%)	2 / 1507 (0.13%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	1 / 427 (0.23%)	0 / 1507 (0.00%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coccidioidomycosis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			

subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningoencephalitis herpetic			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			

subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchitis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 427 (0.23%)	3 / 1507 (0.20%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 427 (0.00%)	2 / 1507 (0.13%)	3 / 1531 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral salt-wasting syndrome			
subjects affected / exposed	0 / 427 (0.00%)	0 / 1507 (0.00%)	1 / 1531 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 1507 (0.07%)	0 / 1531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	235 / 427 (55.04%)	828 / 1507 (54.94%)	822 / 1531 (53.69%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	23 / 427 (5.39%)	59 / 1507 (3.92%)	71 / 1531 (4.64%)
occurrences (all)	27	74	89
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	18 / 427 (4.22%)	143 / 1507 (9.49%)	135 / 1531 (8.82%)
occurrences (all)	24	171	176
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 427 (6.09%)	97 / 1507 (6.44%)	93 / 1531 (6.07%)
occurrences (all)	26	100	94
Eye disorders			

Cataract			
subjects affected / exposed	27 / 427 (6.32%)	119 / 1507 (7.90%)	106 / 1531 (6.92%)
occurrences (all)	33	159	149
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 427 (5.62%)	70 / 1507 (4.64%)	72 / 1531 (4.70%)
occurrences (all)	24	75	75
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 427 (4.68%)	79 / 1507 (5.24%)	76 / 1531 (4.96%)
occurrences (all)	23	88	87
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	45 / 427 (10.54%)	125 / 1507 (8.29%)	125 / 1531 (8.16%)
occurrences (all)	54	145	148
Back pain			
subjects affected / exposed	31 / 427 (7.26%)	82 / 1507 (5.44%)	101 / 1531 (6.60%)
occurrences (all)	32	89	109
Osteoarthritis			
subjects affected / exposed	19 / 427 (4.45%)	81 / 1507 (5.37%)	86 / 1531 (5.62%)
occurrences (all)	22	90	95
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	62 / 427 (14.52%)	190 / 1507 (12.61%)	183 / 1531 (11.95%)
occurrences (all)	85	255	239
Urinary tract infection			
subjects affected / exposed	47 / 427 (11.01%)	178 / 1507 (11.81%)	191 / 1531 (12.48%)
occurrences (all)	78	305	302
Nasopharyngitis			
subjects affected / exposed	22 / 427 (5.15%)	72 / 1507 (4.78%)	90 / 1531 (5.88%)
occurrences (all)	24	88	106
Sinusitis			
subjects affected / exposed	22 / 427 (5.15%)	67 / 1507 (4.45%)	52 / 1531 (3.40%)
occurrences (all)	27	83	62

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2013	The following changes were made as per Amendment 1: Modified the order of the cognitive test battery. Changed the Informed Consent for Project Partner to a Project Partner Acknowledgement Form. Modified the randomization in an amyloid-related imaging abnormalities (ARIA) substudy.
19 March 2014	The following changes were made as per Amendment 2: Changed the timing of the ad hoc magnetic resonance imaging (MRI) done in conjunction with MCI due to AD diagnosis from the first of the 2 consecutive visits to the end of the second Comprehensive Medical Follow-Up Visit. Deleted an inclusion criterion regarding the requirement for vitamin D and calcium. Corrected the description of mandatory risk stratification genetic sample processing. Changed the ARIA substudy to a substudy focused on volumetric MRI changes, and removed ARIA from the list of adverse events of special interest (AESIs).
10 November 2014	The following changes were made as per Amendment 3: Provided sites with an option to consent subjects with a full study informed consent at Visit 1 or a split Screening informed consent at Visit 1 (Screening) and a Study entry informed consent at Visit 2 (Baseline). Extended the visit window for screening to randomization, to provide additional flexibility in scheduling Baseline and Randomization Visits if needed, once risk stratification sample results were obtained from Screening Visit and cognitive battery test results were obtained from Baseline Visit. Provided the option for sites to include subject consent to pharmacogenomics (PGx) research within the main study informed consent form. Replaced the health care resource utilization (HCRU) instrument with the Alzheimer's Disease Cooperative Study—Resource Use Inventory (ADCS-RUI) and updated the schedule of this assessment. Permitted sites to perform the screening visit at a subject's home, after review and approval by the sponsor of the site's procedures, to provide additional flexibility for scheduling and subject comfort. Permitted sites to administer the Clinical Dementia Rating (CDR) assessment prior to the cognitive battery only during the Baseline Visit, and to administer the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change—Mild Cognitive Impairment (ADCS-CGIC-MCI) in parallel with the other cognitive assessments. Reduced the Short Form-36 (SF-36) and European Quality of Life (EQ-5D) assessment schedule.
24 July 2015	The following changes were made as per Amendment 5: Revised treatment effect size assumption. Removed Russia and Italy as countries for site participation. Corrected exclusion criteria numbers 9 and14. Updated excluded medications table to clarify the exclusion of treatment for Parkinson disease. Updated the assessor expectations for the ADCS-RUI assessment.

27 September 2016	The following changes were made as per Amendment 6: Revised the efficacy futility analysis to occur once 33% of events had accrued, rather than at 50%. Added an operational futility analysis to enable an assessment of whether the study could feasibly be completed within an acceptable timeframe, based on the accrual rate of adjudicated cases meeting the event definition. Clarified the timing of required MRI scans and removed the requirement to perform an MRI scan if a scan was performed for the study within the preceding 6 months. Introduced additional options for the performance of the Comprehensive Medical Follow-Up Visit, including the ability to perform assessments during routine Month 6 or Month 12 visits in certain situations and during home visits or by telephone (for project partners) in exceptional circumstances. Made microscopic urine screens standard on all urine sample collections at routine visits rather than as a reflex in the event of abnormalities detected on macroscopic examination. Introduced formal limits for assessment of compliance with study drug to help facilitate consistency in global monitoring and reporting of subjects that were not compliant with administration of study drug. Clarified AESI follow-up and reporting of macular degeneration and hypoglycemia to ensure consistency in follow-up of macular edema and to eliminate ambiguity over reporting of hypoglycemia as an AESI, ensuring consistency across all subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 August 2018	Terminated due to lack of efficacy of the drug and had no safety concern.	-

Notes:

Limitations and caveats

None reported