



Clinical trial results:

Assessment of an Education and Guidance program for Eliquis Adherence in Non-Valvular Atrial Fibrillation (AEGEAN)

Summary

EudraCT number	2013-000055-41
Trial protocol	IT GB ES DE BE
Global end of trial date	20 January 2016

Results information

Result version number	v1 (current)
This version publication date	28 September 2017
First version publication date	28 September 2017

Trial information

Trial identification

Sponsor protocol code	CV185-220
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	20 January 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the impact of educational program on implementation phase adherence in subjects taking apixaban for stroke prevention in atrial fibrillation (SPAF) at 24 weeks.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 65
Country: Number of subjects enrolled	France: 260
Country: Number of subjects enrolled	Spain: 149
Country: Number of subjects enrolled	Italy: 118
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	United Kingdom: 98
Country: Number of subjects enrolled	Germany: 515
Worldwide total number of subjects	1217
EEA total number of subjects	1205

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)	172
From 65 to 84 years	941
85 years and over	104

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1217 participants were enrolled, 1162 randomized (583 Primary SOC, 579 Additional Education Program). 55 were enrolled but not randomized. Reasons for non-randomization include 13 no longer met study criteria, 13 withdrew consent, 3 lost to follow-up, 10 other, and 16 unknown. 1160 were treated (581 Primary SOC, 579 Additional Education Program).

Period 1

Period 1 title	Safety Analysis Set (24 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Primary SOC
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Arm description:

Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.

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

Dosage and administration details:

Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.

Arm title	Additional Educational Program
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Arm description:

Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.

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

Dosage and administration details:

Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.

Number of subjects in period 1	Primary SOC	Additional Educational Program
Started	604	558
Completed	604	558

Period 2

Period 2 title	Primary Efficacy Analysis Set (24 Weeks)
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apixaban (Primary SOC)

Arm description:

Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.

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

Dosage and administration details:

Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.

Arm title	Apixaban (Additional Educational Program)
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Arm description:

Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.

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

Dosage and administration details:

Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 represents the Safety Analysis Set, which categorized subjects according to the counseling they actually received. The Primary Efficacy Analysis Set (24 Weeks) is the baseline period, and represents data for the arms to which subjects were randomized.

Number of subjects in period 2 ^[2]	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)
Started	583	579
Received treatment	581	579
Completed	529	525
Not completed	54	54
Adverse event, serious fatal	6	4
Subject Withdrew Consent	18	21
Adverse event, non-fatal	15	11
Helping Hand not used, treatment taken	1	1
Medical reason	3	3
Inclusion / Exclusion Criterion	2	5
Drug Interruption >30 Consecutive Days	-	2
Lost to follow-up	-	1
Helping Hand not used	2	-
Serious Adverse Event	7	6

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1217 participants were enrolled, 1162 randomized (583 Primary SOC, 579 Additional Education Program). 55 were enrolled but not randomized. Reasons for non-randomization include 13 no longer met study criteria, 13 withdrew consent, 3 lost to follow-up, 10 other, and 16 unknown. 1160 were treated (581 Primary SOC, 579 Additional Education Program).

Period 3

Period 3 title	Safety Analysis Set (48 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Apixaban (Primary SOC)

Arm description:

Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.

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

Dosage and administration details:

Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.

Arm title	Apixaban (Additional Educational Program)
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Arm description:

Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the

Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.	
Arm title	Apixaban (Secondary SOC)

Arm description:

Participants were originally in the Apixaban (AEP) arm and treated with Apixaban 2.5 mg or 5 mg by mouth twice daily and Additional Educational Program (AEP) for the first 24 weeks. After the initial 24-week primary endpoint period participants stopped receiving AEP and were transferred from Apixaban (AEP) arm, stopped the Additional Educational Program (AEP), and switched to the Standard of Care (SOC) information for an additional 24 weeks.

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

Dosage and administration details:

Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.

Number of subjects in period 3	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)	Apixaban (Secondary SOC)
Started	604	308	223
Completed	604	308	223

Period 4

Period 4 title	Primary Efficacy Analysis Set (48 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Apixaban (Primary SOC)
Arm description:	
Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.	
Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.	
Arm title	Apixaban (Additional Educational Program)
Arm description:	
Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.	
Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.	
Arm title	Apixaban (Secondary SOC)
Arm description:	
Participants were originally in the Apixaban (AEP) arm and treated with Apixaban 2.5 mg or 5 mg by mouth twice daily and Additional Educational Program (AEP) for the first 24 weeks. After the initial 24-week primary endpoint period participants stopped receiving AEP and were transferred from Apixaban (AEP) arm, stopped the Additional Educational Program (AEP), and switched to the Standard of Care (SOC) information for an additional 24 weeks.	
Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Apixaban was taken as one tablet twice daily, either 5 mg or 2.5 mg.	

Number of subjects in period 4	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)	Apixaban (Secondary SOC)
Started	529	263	261
Completed	503	250	250
Not completed	80	13	11
Adverse event, serious fatal	7	3	3
Subject Withdrew Consent	21	-	2

Adverse event, non-fatal	17	3	-
Helping Hand not used, treatment taken	3	-	-
Subject decision	1	-	-
Medical reason	4	1	-
Inclusion / Exclusion Criterion	2	-	-
Drug Interruption >30 Consecutive Days	3	-	2
Lost to follow-up	1	-	1
Helping Hand not used	4	-	-
Serious Adverse Event	17	6	3
Joined	54	0	0
Rejoined for follow-up	54	-	-

Baseline characteristics

Reporting groups

Reporting group title	Primary Efficacy Analysis Set (24 Weeks)
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Reporting group description: -

Reporting group values	Primary Efficacy Analysis Set (24 Weeks)	Total	
Number of subjects	1162	1162	
Age Categorical Units: Subjects			
<64	163	163	
64-74	441	441	
>=75	558	558	
Age Continuous Units: years			
arithmetic mean	72.6		
standard deviation	± 8.94	-	
Gender, Male/Female Units: Subjects			
Female	466	466	
Male	696	696	

End points

End points reporting groups

Reporting group title	Primary SOC
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.	
Reporting group title	Additional Educational Program
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.	
Reporting group title	Apixaban (Primary SOC)
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.	
Reporting group title	Apixaban (Additional Educational Program)
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.	
Reporting group title	Apixaban (Primary SOC)
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.	
Reporting group title	Apixaban (Additional Educational Program)
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.	
Reporting group title	Apixaban (Secondary SOC)
Reporting group description: Participants were originally in the Apixaban (AEP) arm and treated with Apixaban 2.5 mg or 5 mg by mouth twice daily and Additional Educational Program (AEP) for the first 24 weeks. After the initial 24-week primary endpoint period participants stopped receiving AEP and were transferred from Apixaban (AEP) arm, stopped the Additional Educational Program (AEP), and switched to the Standard of Care (SOC) information for an additional 24 weeks.	
Reporting group title	Apixaban (Primary SOC)
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and Primary Standard of Care (SOC) information.	
Reporting group title	Apixaban (Additional Educational Program)
Reporting group description: Participants were treated with Apixaban 2.5 mg or 5 mg by mouth twice daily for 48 weeks and the Additional Educational Program (AEP). After the initial 24-week primary endpoint period participants in the Apixaban (AEP) group were randomized 1:1 to continue receiving AEP or stop receiving AEP and revert to Standard of Care (SOC) information via the Apixaban (Secondary SOC) group.	
Reporting group title	Apixaban (Secondary SOC)
Reporting group description: Participants were originally in the Apixaban (AEP) arm and treated with Apixaban 2.5 mg or 5 mg by mouth twice daily and Additional Educational Program (AEP) for the first 24 weeks. After the initial 24-week primary endpoint period participants stopped receiving AEP and were transferred from Apixaban (AEP) arm, stopped the Additional Educational Program (AEP), and switched to the Standard of Care (SOC) information for an additional 24 weeks.	

Primary: Percentage of days with a correct execution of the apixaban dosing regimen

End point title	Percentage of days with a correct execution of the apixaban dosing regimen
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End point description:

The mean percentage of days which subjects maintained adherence to apixaban treatment was measured for each arm. Adherence to apixaban = number of units of adherence *100 / total number of eligible days for the time period from first dose date, up to 169 days. Unit of adherence: A 24-hour window where the treatment is taken as prescribed, ie, 1 tablet (5 mg or 2.5 mg, as appropriate) 2 times a day. If only one dose is missed in 24-hours, it is still considered as a unit of adherence. Adherence up to 24 weeks was calculated as the percentage of adherence units within that period. If a subject discontinued from the study before 24 weeks, the denominator time period was censored at the earlier of last dose date or discontinuation date for discontinuation due to reasons unrelated to subject adherence, such as withdrawn consent, or AE; otherwise, the period was censored at the minimum of 169 days and last dose date + 30 days.

End point type	Primary
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End point timeframe:

Day 1 up to week 24

End point values	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	583	579		
Units: percentage				
arithmetic mean (standard deviation)	91.64 (± 17.143)	91.88 (± 16.14)		

Statistical analyses

Statistical analysis title	Difference in adherence at Week 24
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Statistical analysis description:

t-tests for difference in percentage of adherence at Week 24 between SOC and AEP arms

Comparison groups	Apixaban (Additional Educational Program) v Apixaban (Primary SOC)
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Number of subjects included in analysis	1162
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.8117 ^[1]
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Method	t-test, 2-sided
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Parameter estimate	Difference in Percentage
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Point estimate	-0.24
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-2.18
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upper limit	1.7
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Notes:

[1] - P-value (two-sided) corresponds to the two-sample t-tests for difference in percentage of adherence at Week 24

Secondary: Percentage of days with a correct execution of the apixaban dosing regimen during the 12 to 24 weeks period compared with during the first 12 weeks

End point title	Percentage of days with a correct execution of the apixaban dosing regimen during the 12 to 24 weeks period compared with during the first 12 weeks
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End point description:

The mean adherence to apixaban treatment during the first 24 weeks was measured between the standard of care (SOC) information and Additional Education Program (AEP) arms and expressed as a percentage. Adherence to Apixaban = number of units of adherence *100 / total number of eligible days for the time period.

End point type	Secondary
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End point timeframe:

Day 1 to Week 12, Week 12 to Week 24

End point values	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	525	527		
Units: percentage				
arithmetic mean (standard deviation)				
First Dose to Week 12	93.7 (± 14.18)	93 (± 15.71)		
Week 12 to Week 24	90.3 (± 20.64)	90.9 (± 18.36)		

Statistical analyses

Statistical analysis title	Adherence at 12 Weeks v. 24 Weeks (SOC)
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Statistical analysis description:

Percent adherence at 12 Weeks v. Percent adherence at 24 Weeks for subjects receiving Standard Of Care information

Comparison groups	Apixaban (Additional Educational Program) v Apixaban (Primary SOC)
Number of subjects included in analysis	1052
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [2]
Method	paired t-test

Notes:

[2] - P-value is from a paired t-test comparing percent adherence at 12 and 24 Weeks in the SOC arm. Only participants with available data at both Study Days 85 and 169 are included.

Statistical analysis title	Adherence at 12 Weeks v. 24 Weeks (AEP)
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Statistical analysis description:

Percent adherence at 12 Weeks v. Percent adherence at 24 Weeks for subjects in the Additional Education Program

Comparison groups	Apixaban (Additional Educational Program) v Apixaban
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	(Primary SOC)
Number of subjects included in analysis	1052
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[3]
Method	paired t-test

Notes:

[3] - P-value is from a paired t-test comparing percent adherence at 12 and 24 Weeks in the AEP arm. Only participants with available data at both Study Days 85 and 169 are included.

Secondary: Percentage of days with a correct execution of the Apixaban dosing regimen during the 24 to 48 weeks period

End point title	Percentage of days with a correct execution of the Apixaban dosing regimen during the 24 to 48 weeks period
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End point description:

The mean percentage of days which subjects maintained adherence to apixaban treatment was measured for each arm. Adherence to apixaban = number of units of adherence *100 / total number of eligible days for the time period from first dose date, up to 169 days. Unit of adherence: A 24-hour window where the treatment is taken as prescribed, ie, 1 tablet (5 mg or 2.5 mg, as appropriate) 2 times a day. If only one dose is missed in 24-hours, it is still considered as a unit of adherence. Adherence over 24 weeks was calculated as the percentage of adherence units within that period. If a subject discontinued from the study before 48 weeks, the denominator time period was censored at the earlier of last dose date or discontinuation date for discontinuation due to reasons unrelated to participant adherence, such as withdrawn consent, or AE; otherwise, the period was censored at the minimum of 169 days and last dose date + 30 days.

End point type	Secondary
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End point timeframe:

Week 24 to Week 48

End point values	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)	Apixaban (Secondary SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	510	253	254	
Units: percentage				
arithmetic mean (standard deviation)	87.59 (± 22.921)	88.41 (± 22.148)	87.51 (± 21.125)	

Statistical analyses

Statistical analysis title	Correct apixaban dosing from week 24 to 48
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Statistical analysis description:

Difference of adherence rates during weeks 24 to 48 for Apixaban (Additional Educational Program) v. Apixaban (Secondary SOC)

Comparison groups	Apixaban (Secondary SOC) v Apixaban (Additional Educational Program)
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Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6399 ^[4]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.88
upper limit	4.68

Notes:

[4] - P-values are obtained from the Cochran t-test for pairwise comparison between groups (two-sided).

Statistical analysis title	Correct apixaban dosing from week 24 to 48
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Statistical analysis description:

Difference of adherence rates during weeks 24 to 48 for Apixaban (Secondary SOC) v. Apixaban (Primary SOC)

Comparison groups	Apixaban (Secondary SOC) v Apixaban (Primary SOC)
Number of subjects included in analysis	764
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9616 ^[5]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.45
upper limit	3.29

Notes:

[5] - P-values are obtained from the Cochran t-test for pairwise comparison between groups (two-sided).

Statistical analysis title	Correct apixaban dosing from week 24 to 48
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Statistical analysis description:

Difference of adherence rates during weeks 24 to 48 for Apixaban (Additional Educational Program) v. Apixaban (Primary SOC)

Comparison groups	Apixaban (Additional Educational Program) v Apixaban (Primary SOC)
Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6341 ^[6]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	4.24

Notes:

[6] - P-values are obtained from the Cochran t-test for pairwise comparison between groups (two-sided).

Statistical analysis title	F-test of adherence to apixapan treatment
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Statistical analysis description:

F-test p-value is obtained from the one-way ANOVA model

Comparison groups	Apixaban (Secondary SOC) v Apixaban (Additional Educational Program) v Apixaban (Primary SOC)
Number of subjects included in analysis	1017
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.8707 ^[7]
Method	ANOVA

Notes:

[7] - F-test p-value is obtained from the one-way ANOVA model

Secondary: Non-adherence predictors of 20% or more (vs. at least 80% adherence) at 24 weeks

End point title	Non-adherence predictors of 20% or more (vs. at least 80% adherence) at 24 weeks
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End point description:

Logit analyses were conducted on the Primary Efficacy Set to identify non-adherence predictors of 20% or more (vs. at least 80% adherence) at 24 weeks. In the Primary SOC group, alcohol use, Mini-Mental State Evaluation (MMSE) score, UK standard occupational classification, and type of atrial fibrillation were retained in the model (p-value <= 0.2). In the Additional Educational Program group, alcohol use, type of atrial fibrillation, age and Vitamin K Antagonists (VKA) status were retained in the model (p-value <= 0.2). No variables significantly predicted >= 20% non-adherence at 24 weeks. Odds ratios are presented for predictors of non-adherence.

End point type	Secondary
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End point timeframe:

Week 24

End point values	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	557	560		
Units: Odds ratio				
number (confidence interval 95%)				
<=2 Alcoholic Drink/Day Average vs None	1.251 (0.691 to 2.265)	0.994 (0.558 to 1.682)		
>=3 Alcoholic Drink/Day Average vs None	4.268 (1.226 to 14.859)	3.782 (0.884 to 16.178)		
Mini-mental state examination score	0.808 (0.686 to 0.952)	99999 (99999 to 99999)		

Higher mgmt., adm. and professional jobs vs UKSOC1	0.827 (0.136 to 5.033)	99999 (99999 to 99999)		
Higher professional occupations vs UKSOC1	0.898 (0.197 to 4.091)	99999 (99999 to 99999)		
Intermediate occupations vs UKSOC1	1.23 (0.401 to 3.769)	99999 (99999 to 99999)		
Large employers and mgmt. and adm. jobs vs UKSOC1	2.823 (0.412 to 19.338)	99999 (99999 to 99999)		
Lower mgmt., adm. and professional jobs vs UKSOC1	0.948 (0.256 to 3.515)	99999 (99999 to 99999)		
Lower supervisory and tech. occupations vs UKSOC1	3.587 (1.008 to 12.766)	99999 (99999 to 99999)		
Never worked and long-term unemployed vs UKSOC1	1.289 (0.419 to 3.962)	99999 (99999 to 99999)		
Routine occupations vs UKSOC1	0.508 (0.181 to 1.425)	99999 (99999 to 99999)		
Semi-routine occupations vs UKSOC1	0.45 (0.083 to 2.453)	99999 (99999 to 99999)		
Paroxysmal vs Persistent Atrial Fibrillation	1.626 (0.766 to 3.453)	1.911 (0.94 to 3.885)		
Permanent vs Persistent Atrial Fibrillation	2.56 (1.152 to 5.688)	1.846 (0.819 to 4.158)		
VKA Naïve vs Non-Naïve	99999 (99999 to 99999)	1.686 (0.932 to 3.049)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with serious adverse events (SAEs), drug related adverse events (AE), AE leading to discontinuation, and death (up to 24 weeks)

End point title	Number of participants with serious adverse events (SAEs), drug related adverse events (AE), AE leading to discontinuation, and death (up to 24 weeks)
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End point description:

Safety analyses were done for the Safety Analysis Set, for which subjects were categorized according to the counseling actually received. AEs with onset date from day 1 through week 24 are included in this summary. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, probable, possible, or missing relationship to study drug.

End point type	Secondary
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End point timeframe:

Day 1 up to week 24

End point values	Primary SOC	Additional Educational Program		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	604	558		
Units: Participants				
SAE	75	82		

Drug related AE	54	41		
AE leading to discontinuation	33	22		
Death	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with serious adverse events (SAEs), drug related adverse events (AE), AE leading to discontinuation, and death (24 to 48 weeks)

End point title	Number of participants with serious adverse events (SAEs), drug related adverse events (AE), AE leading to discontinuation, and death (24 to 48 weeks)
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End point description:

Safety analyses were done for the Safety Analysis Set, for which subjects were categorized according to the counseling actually received. Adverse events with onset date after 24 weeks are included in this summary. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, probable, possible, or missing relationship to study drug.

End point type	Secondary
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End point timeframe:

Week 24 up to Week 48

End point values	Apixaban (Primary SOC)	Apixaban (Additional Educational Program)	Apixaban (Secondary SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	604	308	223	
Units: Participants				
SAE	71	43	30	
Drug related AE	15	12	10	
AE leading to discontinuation	14	3	8	
Death	3	3	6	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days of discontinuation of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Primary SOC (Period 1)
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Reporting group description:

Apixaban 2.5 mg or 5 mg by mouth twice daily for 24 weeks and Primary SOC information.

Reporting group title	Continued Additional Educational Program (CAEP) (Period 2)
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Reporting group description:

Subjects enrolled in AEP program during the first 24 weeks continued receiving AEP program up to 48 weeks.

Reporting group title	Additional Educational Program (Period 1)
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Reporting group description:

Apixaban 2.5 mg or 5 mg by mouth twice daily for 24 weeks and Additional Educational Program.

Reporting group title	Secondary SOC (Period 2)
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Reporting group description:

Subjects who received AEP for 24 weeks then revert to SOC after the second randomization.

Reporting group title	Primary SOC (Period 2)
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Reporting group description:

Subjects who received Apixaban 2.5 mg or 5 mg by mouth twice daily for initial 24 weeks and Primary SOC information continued for a period 48 Weeks.

Serious adverse events	Primary SOC (Period 1)	Continued Additional Educational Program (CAEP) (Period 2)	Additional Educational Program (Period 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 604 (11.42%)	40 / 308 (12.99%)	79 / 558 (14.16%)
number of deaths (all causes)	7	6	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma pancreas			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Bronchial carcinoma			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Neuroendocrine carcinoma			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Prostate cancer			
subjects affected / exposed	1 / 604 (0.17%)	1 / 308 (0.32%)	0 / 558 (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
Renal cell carcinoma			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			

subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aneurysm ruptured			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Haemorrhage			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	1 / 604 (0.17%)	2 / 308 (0.65%)	0 / 558 (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
Hypertensive crisis			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Phlebitis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Arthroscopic surgery			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast conserving surgery			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Cancer surgery			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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 ablation			
subjects affected / exposed	8 / 604 (1.32%)	1 / 308 (0.32%)	3 / 558 (0.54%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 604 (0.17%)	1 / 308 (0.32%)	0 / 558 (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
Cardiac pacemaker battery replacement			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac resynchronisation therapy			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Cardioversion			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal transplant			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary angioplasty			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary arterial stent insertion			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery bypass			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart valve replacement			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal endoscopic therapy			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Inguinal hernia repair			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc operation			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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 arthroplasty			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Leg amputation			

subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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 lobectomy			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve replacement			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrectomy			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Percutaneous coronary intervention			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scar excision			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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 operation			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Surgery			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein operation			

subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Transurethral prostatectomy			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 604 (0.17%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug intolerance			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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 malfunction			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Impaired healing			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site haematoma			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-Organ failure			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Social circumstances			
Elderly			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			

Acquired phimosis			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cyst			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Prostatitis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 604 (0.17%)	2 / 308 (0.65%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	4 / 558 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 604 (0.17%)	1 / 308 (0.32%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Respiratory distress			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status asthmaticus			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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 failure			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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			
Arteriogram coronary			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration breast			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Biopsy lung			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood test abnormal			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Catheterisation cardiac			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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 stress test abnormal			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest injury			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Contusion			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Facial bones fracture			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 604 (0.33%)	1 / 308 (0.32%)	3 / 558 (0.54%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Femoral neck fracture			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Traumatic fracture			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 604 (0.33%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 604 (0.17%)	2 / 308 (0.65%)	2 / 558 (0.36%)
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	1 / 604 (0.17%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			

subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Arrhythmia			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	7 / 604 (1.16%)	0 / 308 (0.00%)	10 / 558 (1.79%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Atrial tachycardia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Bradyarrhythmia			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	9 / 604 (1.49%)	3 / 308 (0.97%)	13 / 558 (2.33%)
occurrences causally related to treatment / all	0 / 9	0 / 4	0 / 15
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac flutter			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve disease			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Left ventricular failure			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Myocardial infarction			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Pericardial effusion			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	2 / 604 (0.33%)	1 / 308 (0.32%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	1 / 604 (0.17%)	1 / 308 (0.32%)	0 / 558 (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
Ventricular fibrillation			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal ganglia infarction			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Cerebellar haemorrhage			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Cerebral haematoma			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Dizziness			

subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Epilepsy			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertonia			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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 stroke seizure			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular syndrome			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Seizure			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 604 (0.50%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 604 (0.33%)	1 / 308 (0.32%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Hypofibrinogenaemia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic anaemia			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Spontaneous haematoma			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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 disorders			

Abdominal hernia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Barrett's oesophagus			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Diarrhoea			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Constipation			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Gastritis			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Intestinal haemorrhage			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Cholecystitis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic lesion			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Cholelithiasis			
subjects affected / exposed	2 / 604 (0.33%)	0 / 308 (0.00%)	0 / 558 (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
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cystitis haemorrhagic			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Haematuria			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal disorder			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urethral stenosis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lumbar spinal stenosis			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Mobility decreased			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Muscular weakness			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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 extremity			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	2 / 558 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gangrene			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Erysipelas			
subjects affected / exposed	1 / 604 (0.17%)	0 / 308 (0.00%)	0 / 558 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	0 / 604 (0.00%)	2 / 308 (0.65%)	0 / 558 (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
Pneumonia			
subjects affected / exposed	5 / 604 (0.83%)	1 / 308 (0.32%)	3 / 558 (0.54%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Streptococcal endocarditis			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Urinary tract infection			
subjects affected / exposed	0 / 604 (0.00%)	1 / 308 (0.32%)	0 / 558 (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
Urosepsis			

subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
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			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	1 / 558 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 604 (0.00%)	0 / 308 (0.00%)	0 / 558 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Secondary SOC (Period 2)	Primary SOC (Period 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 223 (13.00%)	62 / 604 (10.26%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			

subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm ruptured			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arthroscopic surgery			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast conserving surgery			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer surgery			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ablation			
subjects affected / exposed	0 / 223 (0.00%)	3 / 604 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker battery replacement			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac resynchronisation therapy			
subjects affected / exposed	1 / 223 (0.45%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardioversion			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal transplant			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary angioplasty			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary arterial stent insertion			

subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve replacement			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal endoscopic therapy			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia repair			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc operation			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint arthroplasty			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg amputation			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung lobectomy			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve replacement			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Percutaneous coronary intervention			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scar excision			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal operation			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein operation			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral prostatectomy			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 223 (0.00%)	3 / 604 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site haematoma			

subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ failure			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Elderly			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Acquired phimosis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cyst			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	2 / 223 (0.90%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	1 / 223 (0.45%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration breast			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy lung			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood test abnormal			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac stress test abnormal			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 223 (0.45%)	3 / 604 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 223 (0.45%)	4 / 604 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac flutter			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 223 (0.90%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia infarction			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 223 (0.45%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertonia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post stroke seizure			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular syndrome			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypofibrinogenaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypochromic anaemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous haematoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Barrett's oesophagus			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 223 (0.00%)	2 / 604 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 223 (0.00%)	2 / 604 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic lesion			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 223 (0.45%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar spinal stenosis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 223 (0.90%)	2 / 604 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal endocarditis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 223 (0.00%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 604 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 604 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Primary SOC (Period 1)	Continued Additional Educational Program (CAEP) (Period 2)	Additional Educational Program (Period 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 604 (6.62%)	5 / 308 (1.62%)	46 / 558 (8.24%)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	40 / 604 (6.62%)	5 / 308 (1.62%)	46 / 558 (8.24%)
occurrences (all)	44	5	47

Non-serious adverse events	Secondary SOC (Period 2)	Primary SOC (Period 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 223 (2.24%)	21 / 604 (3.48%)	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 223 (2.24%)	21 / 604 (3.48%)	
occurrences (all)	5	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2013	Amendment 01 - Addition of an interim analysis - Changes to subject enrollment and exclusion criteria - Minor changes to the study assessments - Additions and deletions to the list of hematology laboratory tests

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported