



Clinical trial results:

Efficacy and Safety Study of Darolutamide (ODM-201) in Men With High-risk Non-metastatic Castration-resistant Prostate Cancer (ARAMIS)

Summary

EudraCT number	2013-003820-36
Trial protocol	SE HU FI LV CZ AT GB SK DE PT IT BE BG FR PL RO LT EE
Global end of trial date	14 June 2021

Results information

Result version number	v1 (current)
This version publication date	18 June 2022
First version publication date	18 June 2022

Trial information

Trial identification

Sponsor protocol code	17712
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02200614
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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	14 June 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the superiority of darolutamide vs. placebo in metastasis-free survival (MFS), in patients with high-risk nmCRPC.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed the informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Androgen deprivation therapy (ADT)

Evidence for comparator: -

Actual start date of recruitment	12 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belarus: 31
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 100
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Canada: 45
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Czechia: 29
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Finland: 45
Country: Number of subjects enrolled	France: 80
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Israel: 1

Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Japan: 95
Country: Number of subjects enrolled	Korea, Republic of: 76
Country: Number of subjects enrolled	Latvia: 62
Country: Number of subjects enrolled	Lithuania: 79
Country: Number of subjects enrolled	Peru: 22
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Portugal: 36
Country: Number of subjects enrolled	Romania: 28
Country: Number of subjects enrolled	Russian Federation: 105
Country: Number of subjects enrolled	Serbia: 8
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Spain: 117
Country: Number of subjects enrolled	Sweden: 22
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Turkey: 27
Country: Number of subjects enrolled	Ukraine: 56
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	United States: 139
Worldwide total number of subjects	1509
EEA total number of subjects	692

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)	197
From 65 to 84 years	1182
85 years and over	130

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 36 countries between 12 September 2014 (first subject first visit) and 14 June 2021 (last subject last visit).

Pre-assignment

Screening details:

From 2696 subjects who signed informed consent, 1187 subjects were discontinued from screening. A total of 1509 subjects were randomly assigned to either darolutamide arm or placebo arm. The study was unblinded on 30 OCT 2018 and subjects in the placebo arm could cross over to open-label darolutamide treatment.

Period 1

Period 1 title	Double blind treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Darolutamide (BAY1841788)

Arm description:

Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

Arm type	Experimental
Investigational medicinal product name	Darolutamide
Investigational medicinal product code	BAY1841788
Other name	ODM-201
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a total daily dose of 1200 mg

Arm title	Placebo
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Arm description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 tablets twice daily with food

Number of subjects in period 1	Darolutamide (BAY1841788)	Placebo
Started	955	554
Completed	591	170
Not completed	364	384
Confirmed metastasis	120	140
Personal reason	77	85
Judgment of the investigator	59	99
Protocol deviation	14	7
Adverse event	86	48
Other reason	6	2
Metastasis by local reading	1	3
Not treated	1	-

Period 2

Period 2 title	Open label
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Darolutamide (BAY1841788)

Arm description:

Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

Arm type	Experimental
Investigational medicinal product name	Darolutamide
Investigational medicinal product code	BAY1841788
Other name	ODM-201
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a total daily dose of 1200 mg

Arm title	Placebo
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Arm description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

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

Number of subjects in period 2	Darolutamide (BAY1841788)	Placebo
Started	591	170
Completed	295	114
Not completed	296	56
Confirmed metastasis	1	-
Personal reason	60	8
Judgment of the investigator	29	2
Protocol deviation	3	2
Adverse event	41	11
Other reason	22	4
Metastasis by local reading	138	27
Missing	2	2

Baseline characteristics

Reporting groups

Reporting group title	Darolutamide (BAY1841788)
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Reporting group description:

Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

Reporting group title	Placebo
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Reporting group description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

Reporting group values	Darolutamide (BAY1841788)	Placebo	Total
Number of subjects	955	554	1509
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	73.9 ± 7.8	73.2 ± 8.2	-
Sex: Female, Male Units: participants			
Female	0	0	0
Male	955	554	1509
Race/Ethnicity, Customized Units: Subjects			
Asia	122	71	193
Black or African American	28	24	52
White	760	434	1194
Missing	36	19	55
Other	9	6	15

End points

End points reporting groups

Reporting group title	Darolutamide (BAY1841788)
Reporting group description: Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).	
Reporting group title	Placebo
Reporting group description: Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).	
Reporting group title	Darolutamide (BAY1841788)
Reporting group description: Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).	
Reporting group title	Placebo
Reporting group description: Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).	

Primary: Metastasis-Free Survival

End point title	Metastasis-Free Survival
End point description: Metastasis-Free Survival (MFS) is defined as the time from randomisation to evidence of metastasis or death from any cause, whichever occurs first (cut-off date 15 Nov 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.	
End point type	Primary
End point timeframe: From randomization to the time approximately 385 MFS events were observed (approximately 48 months)	

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	40.37 (34.33 to 99999)	18.43 (15.51 to 22.34)		

Statistical analyses

Statistical analysis title	Metastasis-Free Survival
Comparison groups	Darolutamide (BAY1841788) v Placebo

Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.413
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.341
upper limit	0.5

Notes:

[1] - Hazard ratio and 95% Confidence Interval (CI) was based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Overall Survival - Primary analysis

End point title	Overall Survival - Primary analysis
End point description:	
Overall Survival (OS) was defined as the time from randomization to death due to any cause. 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.	
End point type	Secondary
End point timeframe:	
From randomization of the first subject to the time approximatively 140 death events were observed (approximately 48 months)	

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	99999 (44.45 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
Primary analysis	
Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.04521
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.706

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.501
upper limit	0.994

Notes:

[2] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to pain progression - Primary analysis

End point title	Time to pain progression - Primary analysis
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End point description:

Time to pain progression (PP) is defined as time from randomization to pain progression, where progression is defined as an increase of 2 or more points from baseline in question 3 of the Brief Pain Inventory-Short Form questionnaire (BPI-SF) related to the worst pain in the last 24 hours taken as a 7-day average for post-baseline scores, or initiation of short or long-acting opioids for pain, whichever comes first. Initiation or change in the use of other non-opioid analgesics is not used in the analysis of pain progression.

End point type	Secondary
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End point timeframe:

From randomization until last study treatment (assessed every 4 months) (approximately 48 months)

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	40.31 (33.21 to 41.20)	25.36 (19.09 to 29.63)		

Statistical analyses

Statistical analysis title	Time to pain progression
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Statistical analysis description:

Primary analysis

Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.000008
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.647

Confidence interval

level	95 %
sides	2-sided
lower limit	0.533
upper limit	0.785

Notes:

[3] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to initiation of first cytotoxic chemotherapy for prostate cancer - Primary analysis

End point title	Time to initiation of first cytotoxic chemotherapy for prostate cancer - Primary analysis
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End point description:

The time to cytotoxic chemotherapy was defined as the time from randomization to the start of the first cytotoxic chemotherapy cycle. 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.

End point type	Secondary
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End point timeframe:

From randomization until last study treatment (assessed every 4 months) (approximately 48 months)

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	38.21 (35.55 to 41.89)		

Statistical analyses

Statistical analysis title	Time to initiation of first cytotoxic chemotherapy
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Statistical analysis description:

Primary analysis

Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.433
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.314
upper limit	0.595

Notes:

[4] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to first symptomatic skeletal event (SSE) - Primary analysis

End point title	Time to first symptomatic skeletal event (SSE) - Primary
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End point description:

The time to the first SSE was defined as the time from randomization to the occurrence of the first SSE. 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.

End point type	Secondary
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End point timeframe:

From randomization until last study treatment (assessed every 4 months) (approximately 48 months)

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to first SSE
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Statistical analysis description:

Primary analysis

Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.011262
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.428
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.218
upper limit	0.842

Notes:

[5] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Overall Survival - Final analysis

End point title	Overall Survival - Final analysis
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End point description:

Overall Survival (OS) was defined as the time from randomization to death due to any cause. The final analysis was done at the time of the data cut-off (15 NOV 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.

End point type	Secondary
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End point timeframe:

From randomization of the first subject to the time approximately 254 death events were observed (approximately 56 months)

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	99999 (56.14 to 99999)	99999 (46.91 to 99999)		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
Final analysis	
Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.003048
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.685
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.533
upper limit	0.881

Notes:

[6] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to pain progression - Final analysis

End point title	Time to pain progression - Final analysis
End point description:	
For time to pain progression, the analysis performed using the primary completion cut-off data (03 SEP 2018) was considered final and no new analysis was performed for time to pain progression.	
End point type	Secondary
End point timeframe:	
From randomization until last study treatment (assessed every 4 months) (approximately 48 months)	

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	40.31 (33.21 to 41.20)	25.36 (19.09 to 29.63)		

Statistical analyses

Statistical analysis title	Time to pain progression
Statistical analysis description:	
Final analysis	
Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.000008
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.647
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.533
upper limit	0.785

Notes:

[7] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to initiation of first cytotoxic chemotherapy for prostate cancer - Final analysis

End point title	Time to initiation of first cytotoxic chemotherapy for prostate cancer - Final analysis
End point description:	
The time to cytotoxic chemotherapy was defined as the time from randomization to the start of the first cytotoxic chemotherapy cycle. The final analysis was done at the time of the data cut-off (15 NOV 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.	
End point type	Secondary
End point timeframe:	
From randomization until initiation of first cytotoxic chemotherapy treatment (approximately 59 months)	

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to initiation of first cytotoxic chemotherapy
Statistical analysis description:	
Final analysis	
Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.000044
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.579
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.444
upper limit	0.755

Notes:

[8] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to first symptomatic skeletal event (SSE) - Final analysis

End point title	Time to first symptomatic skeletal event (SSE) - Final analysis
End point description:	
The time to the first SSE was defined as the time from randomization to the occurrence of the first SSE. The final analysis was done at the time of the data cut-off (15 NOV 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.	
End point type	Secondary
End point timeframe:	
From randomization until occurrence of first SSE event (approximately 59 months)	

End point values	Darolutamide (BAY1841788)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	554		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to first SSE
Statistical analysis description:	
Final analysis	
Comparison groups	Darolutamide (BAY1841788) v Placebo
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.005294
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.484
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.287
upper limit	0.815

Notes:

[9] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 30 days after last treatment (last cut-off date 14 JUN 2021)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Darolutamide (DB)
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Reporting group description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg (double blind [DB]).

Reporting group title	Placebo+Darolutamide (CO)
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Reporting group description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

Reporting group title	Placebo (DB)
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Reporting group description:

Subjects received matching placebo 2 tablets twice daily with food (double blind [DB]).

Reporting group title	Darolutamide (DB+OL)
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Reporting group description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

Serious adverse events	Darolutamide (DB)	Placebo+Darolutamide (CO)	Placebo (DB)
Total subjects affected by serious adverse events			
subjects affected / exposed	251 / 954 (26.31%)	43 / 170 (25.29%)	121 / 554 (21.84%)
number of deaths (all causes)	155	16	137
number of deaths resulting from adverse events	38	6	19
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Basal cell carcinoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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 hepatic neoplasm			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 neoplasm			
subjects affected / exposed	3 / 954 (0.31%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Carcinoid tumour			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Choroid melanoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Colon cancer			
subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Gastric cancer			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	2 / 554 (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
Laryngeal cancer			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Lipoma			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Lymphoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Malignant melanoma in situ			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Meningioma			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Mesothelioma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Metastases to spine			

subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Neoplasm malignant			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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	3 / 954 (0.31%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pituitary tumour			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Rectal adenocarcinoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Rectal cancer			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Renal cancer			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Squamous cell carcinoma			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Thymoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Tumour pain			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung neoplasm malignant			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Prostate cancer			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Brain neoplasm			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Colon neoplasm			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Salivary gland neoplasm			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Rectal neoplasm			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Hepatocellular carcinoma			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Neuroendocrine tumour of the lung			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Aortic dissection			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Aortic stenosis			
subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic thrombosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Arteriosclerosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 / 1
Circulatory collapse			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 / 1
Hypertension			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Hypotension			

subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Lymphoedema			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Thrombosis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Venous thrombosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Subclavian vein thrombosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Iliac artery stenosis			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Embolism			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Surgical and medical procedures			
Angioplasty			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 catheterisation			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Hip arthroplasty			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Inguinal hernia repair			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Orchidectomy			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Transurethral prostatectomy			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Nephrostomy			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Artificial urinary sphincter implant			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Radiotherapy to brain			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Prostatectomy			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Pulmonary resection			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Chest pain			

subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	4 / 954 (0.42%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 1
Gait disturbance			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Pyrexia			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Sudden death			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Sudden cardiac death			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
General physical health deterioration			
subjects affected / exposed	5 / 954 (0.52%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Prostatic obstruction			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 induration			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Perineal pain			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 respiratory failure			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	3 / 554 (0.54%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	3 / 554 (0.54%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Dyspnoea			
subjects affected / exposed	4 / 954 (0.42%)	0 / 170 (0.00%)	2 / 554 (0.36%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Epistaxis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Haemoptysis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Pleural effusion			
subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	1 / 554 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 954 (0.10%)	1 / 170 (0.59%)	0 / 554 (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
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Pulmonary embolism			
subjects affected / exposed	5 / 954 (0.52%)	1 / 170 (0.59%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	1 / 5	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 distress			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 failure			

subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Pulmonary mass			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Depression			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Major depression			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Biopsy prostate			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 creatinine increased			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Body temperature increased			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Prostatic specific antigen increased			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Transaminases increased			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Urine output decreased			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Angiogram			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	2 / 554 (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
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Ankle fracture			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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

Bite			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Facial bones fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Fall			
subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	1 / 554 (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
Femoral neck fracture			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Femur fracture			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Fibula fracture			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Foot fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Fracture			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Hand fracture			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Hip fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Humerus fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Incisional hernia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Ligament sprain			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Multiple injuries			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Patella fracture			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Radiation proctitis			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Radius fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Rib fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Road traffic accident			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Subdural haematoma			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Tibia fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Ulna fracture			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Wrist fracture			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Stenosis of vesicourethral anastomosis			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Thermal burn			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Postoperative ileus			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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 procedure complication			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Heart injury			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Skull fracture			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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 complication			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Flatback syndrome			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Craniocerebral injury			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Incarcerated parastomal hernia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 disorders			
Acute myocardial infarction			
subjects affected / exposed	5 / 954 (0.52%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	4 / 954 (0.42%)	1 / 170 (0.59%)	2 / 554 (0.36%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Aortic valve stenosis			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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

Arrhythmia			
subjects affected / exposed	2 / 954 (0.21%)	1 / 170 (0.59%)	0 / 554 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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 fibrillation			
subjects affected / exposed	8 / 954 (0.84%)	3 / 170 (1.76%)	3 / 554 (0.54%)
occurrences causally related to treatment / all	0 / 11	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Atrioventricular block			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Atrioventricular block second degree			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Bradycardia			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Cardiac arrest			

subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	3 / 554 (0.54%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 3
Cardiac failure			
subjects affected / exposed	8 / 954 (0.84%)	2 / 170 (1.18%)	4 / 554 (0.72%)
occurrences causally related to treatment / all	0 / 9	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 4	0 / 1	0 / 3
Cardiac failure acute			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Conduction disorder			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Coronary artery disease			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Coronary artery stenosis			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Hypertensive heart disease			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 / 1
Myocardial infarction			
subjects affected / exposed	4 / 954 (0.42%)	2 / 170 (1.18%)	2 / 554 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Myocardial ischaemia			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Palpitations			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Sinus bradycardia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Tachycardia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 disorder			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Aortic valve disease			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Cardiovascular insufficiency			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Sinus node dysfunction			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Nervous system disorders			
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Bulbar palsy			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Carotid artery stenosis			
subjects affected / exposed	2 / 954 (0.21%)	1 / 170 (0.59%)	0 / 554 (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
Cerebral infarction			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			

subjects affected / exposed	2 / 954 (0.21%)	1 / 170 (0.59%)	3 / 554 (0.54%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Haemorrhagic stroke			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Myelopathy			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Presyncope			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Seizure			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Syncope			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	2 / 554 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Perineurial cyst			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
IIIrd nerve disorder			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Cognitive disorder			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Ischaemic stroke			
subjects affected / exposed	5 / 954 (0.52%)	1 / 170 (0.59%)	2 / 554 (0.36%)
occurrences causally related to treatment / all	1 / 6	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Partial seizures			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Parkinson's disease			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Vertebrobasilar stroke			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 954 (0.31%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Leukopenia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Lymphopenia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Neutropenia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Autoimmune haemolytic anaemia			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Immune thrombocytopenia			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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 dislocation			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Glaucoma			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Retinal detachment			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Retinal vascular disorder			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Visual impairment			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Macular hole			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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 disorders			
Abdominal mass			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 pain			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Abdominal pain lower			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 upper			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Constipation			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Diarrhoea			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Gastritis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 haemorrhage			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Gastrointestinal necrosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 pain			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Ileus			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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			
subjects affected / exposed	1 / 954 (0.10%)	1 / 170 (0.59%)	0 / 554 (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
Intestinal infarction			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Intestinal obstruction			

subjects affected / exposed	4 / 954 (0.42%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Pancreatic cyst			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Pancreatitis acute			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Plicated tongue			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Proctitis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Rectal haemorrhage			
subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal stenosis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Small intestinal obstruction			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	2 / 554 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Pneumoperitoneum			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Large intestine polyp			

subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	1 / 554 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Enterovesical fistula			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Bowel movement irregularity			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia, obstructive			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Obstructive pancreatitis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Cholangitis acute			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Cholecystitis acute			

subjects affected / exposed	1 / 954 (0.10%)	1 / 170 (0.59%)	1 / 554 (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
Cholecystitis chronic			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Cholelithiasis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Cholestasis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Hepatic function abnormal			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Bile duct stenosis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Biliary obstruction			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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 mass			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Calculus bladder			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Calculus urinary			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Dysuria			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	3 / 554 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	11 / 954 (1.15%)	0 / 170 (0.00%)	7 / 554 (1.26%)
occurrences causally related to treatment / all	0 / 13	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	3 / 954 (0.31%)	2 / 170 (1.18%)	4 / 554 (0.72%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Nephrolithiasis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Oliguria			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Pollakiuria			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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 colic			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Renal failure			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	4 / 554 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Ureteric stenosis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Urinary retention			

subjects affected / exposed	16 / 954 (1.68%)	6 / 170 (3.53%)	20 / 554 (3.61%)
occurrences causally related to treatment / all	1 / 17	0 / 6	1 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract disorder			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Urine flow decreased			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Urinary tract obstruction			
subjects affected / exposed	7 / 954 (0.73%)	1 / 170 (0.59%)	3 / 554 (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
Renal impairment			
subjects affected / exposed	1 / 954 (0.10%)	1 / 170 (0.59%)	0 / 554 (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
Chronic kidney disease			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	2 / 554 (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
Urethral stenosis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Acute kidney injury			
subjects affected / exposed	4 / 954 (0.42%)	1 / 170 (0.59%)	3 / 554 (0.54%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower urinary tract symptoms			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Bladder outlet obstruction			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Ureterolithiasis			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Back pain			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	1 / 554 (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
Flank pain			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Kyphosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Muscular weakness			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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	3 / 954 (0.31%)	0 / 170 (0.00%)	1 / 554 (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
Pain in extremity			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Rheumatoid arthritis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Rotator cuff syndrome			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Spinal pain			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Rapidly progressive osteoarthritis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Spinal stenosis			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Bronchitis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Cellulitis			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	1 / 554 (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
Cellulitis gangrenous			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Dengue fever			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Diverticulitis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Endocarditis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Hepatitis C			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Gastroenteritis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	2 / 554 (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
Infectious mononucleosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Influenza			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Osteomyelitis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Perinephric abscess			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Pneumonia			
subjects affected / exposed	15 / 954 (1.57%)	1 / 170 (0.59%)	6 / 554 (1.08%)
occurrences causally related to treatment / all	0 / 18	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Pneumonia staphylococcal			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Pulmonary tuberculosis			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Pyelonephritis			
subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 954 (0.10%)	1 / 170 (0.59%)	0 / 554 (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
Pyelonephritis acute			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	1 / 554 (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
Sialoadenitis			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Septic shock			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Tick-borne viral encephalitis			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Urinary tract infection			
subjects affected / exposed	7 / 954 (0.73%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Wound infection			
subjects affected / exposed	1 / 954 (0.10%)	1 / 170 (0.59%)	0 / 554 (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
Urosepsis			
subjects affected / exposed	2 / 954 (0.21%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute endocarditis			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Urinary tract infection bacterial			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 sepsis			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Wound abscess			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Klebsiella bacteraemia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Intervertebral discitis			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Abdominal abscess			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Bacterial infection			

subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Arthritis infective			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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 syncytial virus infection			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	1 / 554 (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
Severe acute respiratory syndrome			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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 tract infection			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Cholecystitis infective			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Device related infection			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Medical device site infection			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Varicella zoster virus infection			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Medical device site joint infection			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
COVID-19			
subjects affected / exposed	0 / 954 (0.00%)	1 / 170 (0.59%)	0 / 554 (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
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Suspected COVID-19			
subjects affected / exposed	0 / 954 (0.00%)	0 / 170 (0.00%)	0 / 554 (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
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Dehydration			
subjects affected / exposed	2 / 954 (0.21%)	0 / 170 (0.00%)	0 / 554 (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
Diabetes mellitus			

subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Hyperglycaemia			
subjects affected / exposed	3 / 954 (0.31%)	0 / 170 (0.00%)	1 / 554 (0.18%)
occurrences causally related to treatment / all	0 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Hypoglycaemia			
subjects affected / exposed	1 / 954 (0.10%)	0 / 170 (0.00%)	0 / 554 (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
Decreased appetite			
subjects affected / exposed	4 / 954 (0.42%)	0 / 170 (0.00%)	0 / 554 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Darolutamide (DB+OL)		
Total subjects affected by serious adverse events			
subjects affected / exposed	367 / 954 (38.47%)		
number of deaths (all causes)	224		
number of deaths resulting from adverse events	63		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Benign hepatic neoplasm				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder cancer				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder neoplasm				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Bladder transitional cell carcinoma				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carcinoid tumour				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Choroid melanoma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diffuse large B-cell lymphoma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				

subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal cancer				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipoma				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphoma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma in situ				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mesothelioma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to spine				

subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm malignant			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Pituitary tumour			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal cancer			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal cancer			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thymoma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stromal tumour				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colorectal adenocarcinoma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adenocarcinoma pancreas				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuroendocrine carcinoma				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				

subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Brain neoplasm				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon neoplasm				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salivary gland neoplasm				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal neoplasm				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular carcinoma				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuroendocrine tumour of the lung				

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic dissection			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic stenosis			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Aortic thrombosis			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lymphoedema				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subclavian vein thrombosis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Iliac artery stenosis				

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Angioplasty			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder catheterisation			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip arthroplasty			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia repair			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orchidectomy			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transurethral prostatectomy			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrostomy			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary angioplasty			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Artificial urinary sphincter implant			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiotherapy to brain			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatectomy			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary resection			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			

subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	6 / 954 (0.63%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 6		
Gait disturbance			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sudden cardiac death			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	7 / 954 (0.73%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 4		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Benign prostatic hyperplasia				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostatic obstruction				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate induration				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perineal pain				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 954 (0.52%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			

Epistaxis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary artery thrombosis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	7 / 954 (0.73%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 2			
Pulmonary thrombosis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Biopsy prostate			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood creatinine increased			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Body temperature increased			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatic specific antigen increased			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urine output decreased			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angiocardiogram			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ankle fracture			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Bite				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand fracture				

subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Hip fracture				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple injuries				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Patella fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiation proctitis				

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Subdural haematoma				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stenosis of vesicourethral anastomosis				

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative ileus				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular procedure complication				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Heart injury				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skull fracture				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular graft complication				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Flatback syndrome				

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Incarcerated parastomal hernia			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	6 / 954 (0.63%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Angina pectoris			
subjects affected / exposed	4 / 954 (0.42%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Angina unstable			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic valve stenosis			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Arrhythmia				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis coronary artery				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	9 / 954 (0.94%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block second degree				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				

subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cardiac failure			
subjects affected / exposed	12 / 954 (1.26%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 7		
Cardiac failure acute			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Conduction disorder			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	4 / 954 (0.42%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Coronary artery occlusion			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive heart disease			

subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	11 / 954 (1.15%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 3		
Myocardial ischaemia			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorder			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic valve disease			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiovascular insufficiency			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sinus node dysfunction			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bulbar palsy			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			

subjects affected / exposed	6 / 954 (0.63%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myelopathy				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Normal pressure hydrocephalus				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Perineurial cyst				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
IIIrd nerve disorder				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	5 / 954 (0.52%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 1			
Partial seizures				

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parkinson's disease			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebrobasilar stroke			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 954 (0.84%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenia			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device dislocation			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device occlusion			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal vascular disorder			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Visual impairment			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Macular hole			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			

subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Enterocolitis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal necrosis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal pain				

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Incarcerated inguinal hernia				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal infarction				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Intestinal ischaemia				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Intestinal obstruction				

subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic cyst				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Plicated tongue				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Rectal stenosis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Umbilical hernia				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumoperitoneum				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal haemorrhage				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				

subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enterovesical fistula			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bowel movement irregularity			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus hernia, obstructive			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive pancreatitis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis acute			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bile duct stenosis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary obstruction			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin mass			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calculus bladder			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Calculus urinary			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysuria			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	25 / 954 (2.62%)		
occurrences causally related to treatment / all	0 / 29		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	8 / 954 (0.84%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Nephritis			

subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oliguria				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pollakiuria				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Ureteric obstruction				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ureteric stenosis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				

subjects affected / exposed	33 / 954 (3.46%)		
occurrences causally related to treatment / all	1 / 37		
deaths causally related to treatment / all	0 / 0		
Urinary tract disorder			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urine flow decreased			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	11 / 954 (1.15%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urethral stenosis			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	7 / 954 (0.73%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Lower urinary tract symptoms			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder outlet obstruction			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kyphosis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			

subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rheumatoid arthritis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rapidly progressive osteoarthritis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal stenosis				

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis gangrenous			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Erysipelas			

subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatitis C				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious mononucleosis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Meningitis bacterial				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Osteomyelitis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Perinephric abscess				

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	20 / 954 (2.10%)			
occurrences causally related to treatment / all	0 / 24			
deaths causally related to treatment / all	0 / 3			
Pneumonia pneumococcal				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	3 / 954 (0.31%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Sialoadenitis				

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Tick-borne viral encephalitis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	12 / 954 (1.26%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Vestibular neuronitis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	2 / 954 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	4 / 954 (0.42%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Acute endocarditis				

subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal sepsis				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound abscess				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella bacteraemia				
subjects affected / exposed	0 / 954 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral discitis				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	1 / 954 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				

subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthritis infective			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Severe acute respiratory syndrome			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis infective			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medical device site infection			
subjects affected / exposed	0 / 954 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella zoster virus infection			

subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Medical device site joint infection			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	4 / 954 (0.42%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 3		
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	4 / 954 (0.42%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Suspected COVID-19			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dehydration			
subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			

subjects affected / exposed	2 / 954 (0.21%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	3 / 954 (0.31%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 954 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	4 / 954 (0.42%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Darolutamide (DB)	Placebo+Darolutamide (CO)	Placebo (DB)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	673 / 954 (70.55%)	110 / 170 (64.71%)	354 / 554 (63.90%)
Vascular disorders			
Hypertension			
subjects affected / exposed	66 / 954 (6.92%)	6 / 170 (3.53%)	31 / 554 (5.60%)
occurrences (all)	86	7	39
Hot flush			
subjects affected / exposed	54 / 954 (5.66%)	3 / 170 (1.76%)	25 / 554 (4.51%)
occurrences (all)	58	3	25
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	37 / 954 (3.88%)	7 / 170 (4.12%)	20 / 554 (3.61%)
occurrences (all)	42	8	23
Fatigue			
subjects affected / exposed	126 / 954 (13.21%)	9 / 170 (5.29%)	47 / 554 (8.48%)
occurrences (all)	164	9	60
Oedema peripheral			
subjects affected / exposed	43 / 954 (4.51%)	4 / 170 (2.35%)	17 / 554 (3.07%)
occurrences (all)	49	4	19
Pyrexia			
subjects affected / exposed	18 / 954 (1.89%)	5 / 170 (2.94%)	5 / 554 (0.90%)
occurrences (all)	25	9	7
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	21 / 954 (2.20%)	1 / 170 (0.59%)	6 / 554 (1.08%)
occurrences (all)	21	1	6
Pelvic pain			
subjects affected / exposed	13 / 954 (1.36%)	1 / 170 (0.59%)	12 / 554 (2.17%)
occurrences (all)	15	1	13
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 954 (3.04%)	6 / 170 (3.53%)	11 / 554 (1.99%)
occurrences (all)	34	6	11
Dyspnoea			
subjects affected / exposed	26 / 954 (2.73%)	2 / 170 (1.18%)	16 / 554 (2.89%)
occurrences (all)	28	3	22
Psychiatric disorders			
Insomnia			
subjects affected / exposed	26 / 954 (2.73%)	8 / 170 (4.71%)	11 / 554 (1.99%)
occurrences (all)	28	8	11
Depression			
subjects affected / exposed	20 / 954 (2.10%)	2 / 170 (1.18%)	9 / 554 (1.62%)
occurrences (all)	20	2	10
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed occurrences (all)	6 / 954 (0.63%) 8	6 / 170 (3.53%) 9	1 / 554 (0.18%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	12 / 954 (1.26%) 16	6 / 170 (3.53%) 10	1 / 554 (0.18%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	23 / 954 (2.41%) 32	3 / 170 (1.76%) 3	14 / 554 (2.53%) 19
Weight decreased subjects affected / exposed occurrences (all)	40 / 954 (4.19%) 42	8 / 170 (4.71%) 8	14 / 554 (2.53%) 17
Weight increased subjects affected / exposed occurrences (all)	14 / 954 (1.47%) 15	3 / 170 (1.76%) 3	7 / 554 (1.26%) 8
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	41 / 954 (4.30%) 44	7 / 170 (4.12%) 8	23 / 554 (4.15%) 27
Rib fracture subjects affected / exposed occurrences (all)	16 / 954 (1.68%) 17	6 / 170 (3.53%) 6	8 / 554 (1.44%) 10
Contusion subjects affected / exposed occurrences (all)	12 / 954 (1.26%) 17	2 / 170 (1.18%) 2	2 / 554 (0.36%) 2
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	19 / 954 (1.99%) 20	3 / 170 (1.76%) 4	6 / 554 (1.08%) 8
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	39 / 954 (4.09%) 47	2 / 170 (1.18%) 2	14 / 554 (2.53%) 17
Headache subjects affected / exposed occurrences (all)	41 / 954 (4.30%) 59	4 / 170 (2.35%) 7	14 / 554 (2.53%) 15
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	60 / 954 (6.29%) 76	7 / 170 (4.12%) 7	28 / 554 (5.05%) 33
Neutropenia subjects affected / exposed occurrences (all)	13 / 954 (1.36%) 17	2 / 170 (1.18%) 2	4 / 554 (0.72%) 4
Eye disorders Cataract subjects affected / exposed occurrences (all)	11 / 954 (1.15%) 11	4 / 170 (2.35%) 4	5 / 554 (0.90%) 6
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	25 / 954 (2.62%) 27	2 / 170 (1.18%) 2	12 / 554 (2.17%) 14
Abdominal pain upper subjects affected / exposed occurrences (all)	14 / 954 (1.47%) 16	3 / 170 (1.76%) 3	14 / 554 (2.53%) 15
Diarrhoea subjects affected / exposed occurrences (all)	69 / 954 (7.23%) 87	15 / 170 (8.82%) 16	33 / 554 (5.96%) 37
Constipation subjects affected / exposed occurrences (all)	65 / 954 (6.81%) 70	8 / 170 (4.71%) 11	36 / 554 (6.50%) 41
Nausea subjects affected / exposed occurrences (all)	53 / 954 (5.56%) 59	6 / 170 (3.53%) 6	32 / 554 (5.78%) 37
Vomiting subjects affected / exposed occurrences (all)	17 / 954 (1.78%) 19	3 / 170 (1.76%) 3	10 / 554 (1.81%) 12
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	17 / 954 (1.78%) 20	2 / 170 (1.18%) 4	12 / 554 (2.17%) 14
Rash subjects affected / exposed occurrences (all)	17 / 954 (1.78%) 17	2 / 170 (1.18%) 2	4 / 554 (0.72%) 4
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	24 / 954 (2.52%)	5 / 170 (2.94%)	27 / 554 (4.87%)
occurrences (all)	27	5	30
Haematuria			
subjects affected / exposed	37 / 954 (3.88%)	12 / 170 (7.06%)	27 / 554 (4.87%)
occurrences (all)	48	13	39
Nephrolithiasis			
subjects affected / exposed	14 / 954 (1.47%)	3 / 170 (1.76%)	4 / 554 (0.72%)
occurrences (all)	17	3	4
Nocturia			
subjects affected / exposed	17 / 954 (1.78%)	2 / 170 (1.18%)	10 / 554 (1.81%)
occurrences (all)	17	2	10
Pollakiuria			
subjects affected / exposed	41 / 954 (4.30%)	4 / 170 (2.35%)	18 / 554 (3.25%)
occurrences (all)	46	4	20
Urinary incontinence			
subjects affected / exposed	15 / 954 (1.57%)	3 / 170 (1.76%)	14 / 554 (2.53%)
occurrences (all)	15	3	14
Urinary retention			
subjects affected / exposed	25 / 954 (2.62%)	1 / 170 (0.59%)	24 / 554 (4.33%)
occurrences (all)	27	1	29
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	92 / 954 (9.64%)	9 / 170 (5.29%)	52 / 554 (9.39%)
occurrences (all)	104	9	59
Arthralgia			
subjects affected / exposed	106 / 954 (11.11%)	17 / 170 (10.00%)	58 / 554 (10.47%)
occurrences (all)	146	19	69
Muscle spasms			
subjects affected / exposed	19 / 954 (1.99%)	0 / 170 (0.00%)	4 / 554 (0.72%)
occurrences (all)	20	0	4
Myalgia			
subjects affected / exposed	18 / 954 (1.89%)	2 / 170 (1.18%)	7 / 554 (1.26%)
occurrences (all)	21	3	8
Osteoarthritis			

subjects affected / exposed occurrences (all)	16 / 954 (1.68%) 20	3 / 170 (1.76%) 3	3 / 554 (0.54%) 3
Pain in extremity subjects affected / exposed occurrences (all)	60 / 954 (6.29%) 79	5 / 170 (2.94%) 6	19 / 554 (3.43%) 25
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	13 / 954 (1.36%) 17	3 / 170 (1.76%) 3	9 / 554 (1.62%) 10
Influenza subjects affected / exposed occurrences (all)	28 / 954 (2.94%) 33	2 / 170 (1.18%) 2	8 / 554 (1.44%) 8
Nasopharyngitis subjects affected / exposed occurrences (all)	39 / 954 (4.09%) 50	8 / 170 (4.71%) 11	23 / 554 (4.15%) 27
Pneumonia subjects affected / exposed occurrences (all)	10 / 954 (1.05%) 11	3 / 170 (1.76%) 3	5 / 554 (0.90%) 5
Urinary tract infection subjects affected / exposed occurrences (all)	44 / 954 (4.61%) 59	12 / 170 (7.06%) 12	31 / 554 (5.60%) 37
Upper respiratory tract infection subjects affected / exposed occurrences (all)	26 / 954 (2.73%) 29	3 / 170 (1.76%) 7	10 / 554 (1.81%) 13
COVID-19 subjects affected / exposed occurrences (all)	0 / 954 (0.00%) 0	4 / 170 (2.35%) 4	0 / 554 (0.00%) 0
Metabolism and nutrition disorders			
Hyperkalaemia subjects affected / exposed occurrences (all)	16 / 954 (1.68%) 24	0 / 170 (0.00%) 0	9 / 554 (1.62%) 10
Hypokalaemia subjects affected / exposed occurrences (all)	10 / 954 (1.05%) 10	4 / 170 (2.35%) 4	2 / 554 (0.36%) 2
Decreased appetite			

subjects affected / exposed	30 / 954 (3.14%)	1 / 170 (0.59%)	16 / 554 (2.89%)
occurrences (all)	34	1	18

Non-serious adverse events	Darolutamide (DB+OL)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	742 / 954 (77.78%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	87 / 954 (9.12%)		
occurrences (all)	117		
Hot flush			
subjects affected / exposed	67 / 954 (7.02%)		
occurrences (all)	73		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 954 (4.51%)		
occurrences (all)	53		
Fatigue			
subjects affected / exposed	142 / 954 (14.88%)		
occurrences (all)	198		
Oedema peripheral			
subjects affected / exposed	57 / 954 (5.97%)		
occurrences (all)	67		
Pyrexia			
subjects affected / exposed	21 / 954 (2.20%)		
occurrences (all)	28		
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	30 / 954 (3.14%)		
occurrences (all)	30		
Pelvic pain			
subjects affected / exposed	16 / 954 (1.68%)		
occurrences (all)	19		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	33 / 954 (3.46%) 38		
Dyspnoea subjects affected / exposed occurrences (all)	32 / 954 (3.35%) 34		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	35 / 954 (3.67%) 38		
Depression subjects affected / exposed occurrences (all)	25 / 954 (2.62%) 27		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	13 / 954 (1.36%) 16		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	23 / 954 (2.41%) 29		
Blood creatinine increased subjects affected / exposed occurrences (all)	37 / 954 (3.88%) 51		
Weight decreased subjects affected / exposed occurrences (all)	65 / 954 (6.81%) 72		
Weight increased subjects affected / exposed occurrences (all)	25 / 954 (2.62%) 27		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	62 / 954 (6.50%) 69		
Rib fracture subjects affected / exposed occurrences (all)	28 / 954 (2.94%) 30		

Contusion subjects affected / exposed occurrences (all)	21 / 954 (2.20%) 26		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	26 / 954 (2.73%) 30		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	48 / 954 (5.03%) 64 53 / 954 (5.56%) 75		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	93 / 954 (9.75%) 136 21 / 954 (2.20%) 27		
Eye disorders Cataract subjects affected / exposed occurrences (all)	15 / 954 (1.57%) 16		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation	35 / 954 (3.67%) 39 16 / 954 (1.68%) 19 87 / 954 (9.12%) 114		

subjects affected / exposed	84 / 954 (8.81%)		
occurrences (all)	94		
Nausea			
subjects affected / exposed	60 / 954 (6.29%)		
occurrences (all)	76		
Vomiting			
subjects affected / exposed	21 / 954 (2.20%)		
occurrences (all)	24		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	22 / 954 (2.31%)		
occurrences (all)	25		
Rash			
subjects affected / exposed	24 / 954 (2.52%)		
occurrences (all)	27		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	32 / 954 (3.35%)		
occurrences (all)	37		
Haematuria			
subjects affected / exposed	66 / 954 (6.92%)		
occurrences (all)	96		
Nephrolithiasis			
subjects affected / exposed	21 / 954 (2.20%)		
occurrences (all)	25		
Nocturia			
subjects affected / exposed	23 / 954 (2.41%)		
occurrences (all)	24		
Pollakiuria			
subjects affected / exposed	51 / 954 (5.35%)		
occurrences (all)	63		
Urinary incontinence			
subjects affected / exposed	24 / 954 (2.52%)		
occurrences (all)	25		
Urinary retention			

subjects affected / exposed	39 / 954 (4.09%)		
occurrences (all)	47		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	118 / 954 (12.37%)		
occurrences (all)	142		
Arthralgia			
subjects affected / exposed	135 / 954 (14.15%)		
occurrences (all)	190		
Muscle spasms			
subjects affected / exposed	20 / 954 (2.10%)		
occurrences (all)	21		
Myalgia			
subjects affected / exposed	24 / 954 (2.52%)		
occurrences (all)	28		
Osteoarthritis			
subjects affected / exposed	26 / 954 (2.73%)		
occurrences (all)	33		
Pain in extremity			
subjects affected / exposed	71 / 954 (7.44%)		
occurrences (all)	105		
Infections and infestations			
Bronchitis			
subjects affected / exposed	23 / 954 (2.41%)		
occurrences (all)	30		
Influenza			
subjects affected / exposed	36 / 954 (3.77%)		
occurrences (all)	42		
Nasopharyngitis			
subjects affected / exposed	56 / 954 (5.87%)		
occurrences (all)	78		
Pneumonia			
subjects affected / exposed	22 / 954 (2.31%)		
occurrences (all)	24		
Urinary tract infection			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>COVID-19</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>73 / 954 (7.65%)</p> <p>130</p> <p>34 / 954 (3.56%)</p> <p>40</p> <p>6 / 954 (0.63%)</p> <p>6</p>		
<p>Metabolism and nutrition disorders</p> <p>Hyperkalaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypokalaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>22 / 954 (2.31%)</p> <p>32</p> <p>12 / 954 (1.26%)</p> <p>13</p> <p>40 / 954 (4.19%)</p> <p>49</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2014	Main modifications: • The definition of progression in soft tissue was clarified, excluding progression in lymph nodes in the pelvis below the aortic bifurcation. • An inclusion criterion related to PSA values was amended to allow patients with CRPC defined as "3 rising PSA values at least 1 week apart during ADT" to enter the study. The observation period of PSA values that could be used in the calculation of PSADT was prolonged from 6 to 12 months. • PFS was added as an additional exploratory endpoint. • The collection period of pain data was corrected to continue until documented pain progression and question 7 of Brief Pain Inventory-Short form (BPI-SF) was deleted. The pain medication data was to be collected using case report forms (CRFs) only. • The 3 consecutive blood pressure, heart rate, and electrocardiogram (ECG) recordings were amended to be performed within approximately 5 minutes. • Suspected disease progression was added as a reason for an unscheduled visit. Chest, abdomen and pelvic CT/MRI or x-ray and bone scan were added as options for assessments that could be performed at the unscheduled visit, if indicated. • Use of antineoplastic therapies was clarified. An instruction was added that another systemic antineoplastic therapy could be initiated no sooner than 7 days after the last dose of study treatment. The end-of-study treatment visit was changed to take place 28 days after the last dose (instead of 7 days) for patients who permanently discontinue study treatment and start subsequent antineoplastic therapy. • It was clarified to exclude patients using osteoclast-targeted therapy for prevention of skeletal-related events and to allow those using this therapy for osteoporosis at a dose and schedule indicated for osteoporosis. The minimum duration of this therapy for osteoporosis was deleted. • Withdrawal at the investigator's discretion was added as a reason for discontinuation.
19 July 2016	The protocol was updated to reflect the sponsorship change from Orion to Bayer, and to update information about the study number and study drug nomenclature. Other main modifications were: • Clarifications on inclusion and exclusion criteria were made. • Requirements for monitoring drug-drug interactions were revised.
26 February 2018	Main modifications: • The assumption for the treatment effect size of a hazard ratio of 0.75 requiring 572 MFS events was revised and changed to a larger assumed treatment effect size of 0.65 requiring approximately 385 MFS events. Statistical analyses of primary and secondary endpoints were also modified. The analysis of the primary efficacy endpoint was referred to as MFS analysis throughout the protocol. It was also clarified that secondary endpoints are to be evaluated at the time of the MFS analysis, and at a later time point. • The possibility to receive open-label darolutamide treatment was added, to allow patients who are on darolutamide/placebo treatment at the time of study treatment code unblinding to continue open-label darolutamide treatment at the discretion of the investigator, if the study results support a positive benefit/risk assessment for darolutamide in the study by judgment of the sponsor (considering feedback from the study steering committee and/or health authorities). • Assessments for patients who continue on open-label darolutamide treatment were added. • A standard guidance text was added stating that recording of contrast media as concomitant medication is not required unless there was an AE related to its administration. • Additional survival sweeps were added, to occur shortly after the database cut-off date for the MFS analysis and prior to any subsequent analysis of OS to ensure that OS data are current.

06 July 2019	<p>Main modifications:</p> <ul style="list-style-type: none"> • The option for patients currently receiving treatment in this study to continue treatment in a roll-over study and respective statistical considerations were added to enable patients receiving darolutamide treatment continue to receive darolutamide treatment when the study is completed. The end of study was also defined for completeness and clarity. • The recommendation to avoid concomitant use of moderate CYP3A4 inducers was removed (while strong CYP3A4 inducers should still be avoided). Recent results of the darolutamide exposure-response relationship showed a flat relationship (maximum PSA response) over the entire exposure range of 600 mg b.i.d. and also at exposures below that range. Thus, even with a darolutamide exposure decrease of 50% (potentially driven by a CYP3A4 inducer), there would still be sufficient effect on PSA. • Open-label study wording was updated to describe the endpoint of the study visits and follow up, to describe the local and central reading requirements for metastasis assessments, to add guidance related to discontinuation of study treatment and to clarify the time points of ECG collection.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported