Clinical trial results:
A randomized, double-blind, placebo-controlled Phase III study of darolutamide (ODM-201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer

Summary

EudraCT number	2015-002590-38
Trial protocol	GB SE BE ES FI DE CZ NL PL FR BG IT
Global end of trial date	11 April 2023

Results information

Result version number	v1 (current)
This version publication date	10 April 2024
First version publication date	10 April 2024

Trial information

Trial identification

Sponsor protocol code	BAY1841788/17777

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02799602
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	11 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority in overall survival (OS) of darolutamide in addition to standard androgen deprivation therapy (ADT) and docetaxel over placebo in addition to standard ADT and docetaxel.

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 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:

ADT of the investigator’s choice (luteinizing hormone-releasing hormone [LHRH] agonist/antagonist or orchiectomy) as standard therapy, started ≤12 weeks before randomization. Docetaxel at a dose of 75 mg/m2 as an intravenous infusion every 21 days for 6 cycles, starting within 6 weeks after the start of the study drug, and in combination with prednisone/prednisolone at the discretion of the investigator.

Evidence for comparator: -

Actual start date of recruitment	30 November 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	59 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Brazil: 53
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	China: 203
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Finland: 24
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Italy: 17

Country: Number of subjects enrolled	Japan: 148
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 33
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Russian Federation: 91
Country: Number of subjects enrolled	Korea, Republic of: 85
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	Sweden: 35
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	United States: 218
Worldwide total number of subjects	1305
EEA total number of subjects	352

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)	477
From 65 to 84 years	821
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

This multinational study was conducted between 30-Nov-2016 First Subject First Visit and 11-Apr-2023 Last Subject Last Visit in 23 countries/regions: Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Finland, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Poland, Russia, South Korea, Spain, Sweden, Taiwan, UK and US

Pre-assignment

Screening details:

1306 subjects were randomly assigned in a 1:1 ratio to study treatment and 1305 subjects were considered valid for efficacy analyses. A total of 1302 subjects started treatment and were included to safety analyses.

Period 1

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

Blinding implementation details:

Double-blind

Arms

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

Arm description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started ≤12 weeks before randomization.

Arm type	Experimental
Investigational medicinal product name	Darolutamide (Nubeqa, BAY1841788)
Investigational medicinal product code	BAY1841788
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg.

Arm title	Placebo + Docetaxel

Arm description:

Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started ≤12 weeks before randomization.

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

Dosage and administration details:
The dosing of placebo is the same as for darolutamide

Number of subjects in period 1	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel
Started	651	654
Started treatment	651	651
Completed	0	0
Not completed	651	654
Progressive disease – radiological progression	90	133
Adverse event, serious fatal	9	5
Physician decision	5	6
AE associated with clinical disease progression	24	26
AE not associated w/ clinical disease progression	49	27
Progressive disease – clinical progression	131	276
Consent withdrawn by subject	26	40
Other	287	118
Study drug never administered	-	3
Non-compliance with study drug	14	12
Lost to follow-up	4	2
Protocol deviation	1	-
Additional primary malignancy	11	6

Baseline characteristics

Reporting groups	
Reporting group title	Darolutamide (BAY1841788) + Docetaxel
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 in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started ≤12 weeks before randomization.	
Reporting group title	Placebo + Docetaxel
Reporting group description:	
Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started ≤12 weeks before randomization.	

Reporting group values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel	Total
Number of subjects	651	654	1305
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	243	234	477
>=65 years	408	420	828
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	651	654	1305
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	40	49	89
Not Hispanic or Latino	561	557	1118
Unknown or Not Reported	50	48	98
Race (NIH/OMB)			
More than one race includes: "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander", and "Multiple"			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	231	245	476
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	26	28	54
White	345	333	678
More than one race	6	2	8
Unknown or Not Reported	43	46	89

End points reporting groups

Reporting group title	Darolutamide (BAY1841788) + Docetaxel

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 in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started ≤12 weeks before randomization.

Reporting group title	Placebo + Docetaxel

Reporting group description:

Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started ≤12 weeks before randomization.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were randomized were included in the FAS

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who received at least 1 dose of darolutamide or placebo were included in the SAF.
Subjects were included in the darolutamide+docetaxel arm if they received any dose of darolutamide and were included in the placebo+docetaxel arm if they only received the placebo.

Primary: OS from date of randomization until death from any cause - Number of events

End point title	OS from date of randomization until death from any cause - Number of events

End point description:

Overall survival (OS) was defined as the time from the date of randomization until death from any cause.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

Long-term (Survival) follow-up period: After Active follow-up, patients continued to be contacted approximately every 12 weeks by phone. The end of the Survival follow-up period was defined as when the patient died, was lost to follow-up, withdrew consent, or at the end-of-study.

End point type	Primary

End point timeframe:

From randomization of the first subject until death from any cause up to 25 OCT 2021 cut-off date 533 OS events were reached (approximate 59 months)

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[1]	654[2]		
Units: Subjects				
Number of subjects with event	229	304		
Number of subjects censored	422	350		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	OS - Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.675
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.568
upper limit	0.801

Notes:

[3] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

[4] - One-sided p-value.

Primary: OS from date of randomization until death from any cause - Month

End point title	OS from date of randomization until death from any cause - Month[5]

End point description:

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

Long-term (Survival) follow-up period: After Active follow-up, patients continued to be contacted approximately every 12 weeks by phone. The end of the Survival follow-up period was defined as when the patient died, was lost to follow-up, withdrew consent, or at the end-of-study.
Median, percentile and other 95% CIs were computed using Kaplan-Meier estimates.

99999 = Value cannot be estimated due to censored

End point type	Primary

End point timeframe:

From randomization of the first subject until death from any cause up to 25 OCT 2021 cut-off date 533 OS events were reached (approximate 59 months)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Refer to inferential statistics table above under endpoint "Primary: OS from date of randomization until death from any cause - Number of events".

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[6]	654[7]		
Units: Month				
median (confidence interval 95%)	99999 (99999 to 99999)	48.9 (44.4 to 99999)		

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with TEAEs

End point title	Number of subjects with TEAEs

End point description:

TEAEs = Treatment-emergent adverse events, were defined as any event(s) arising or worsening after the first dose of darolutamide or placebo, until 30 days after the last dose of darolutamide or placebo administration.

Number of Subjects Analyzed for arm "Darolutamide (BAY1841788) + Docetaxel" should be 652. One subject was randomized to the placebo+docetaxel arm but received at least one dose of darolutamide. This subject was included in the darolutamide+docetaxel arm in the analysis of all safety variables

End point type	Secondary

End point timeframe:

From the first dose of darolutamide or placebo until 30 days after the last dose of darolutamide or placebo administration up to cut-off date for the final completion analysis 11 APR 2023 (approximately 77 months)

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[8]	650[9]		
Units: Subjects				
Any TEAE	649	643		
TESAE	306	276		
TEAE leading to study drug dose modification	172	112		
TEAE leading to permanent stop of study drug	90	69		

TEAE leading to docetaxel dose modification	216	214		
TEAE leading to permanent stop of docetaxel	52	67		
Related to protocol-required procedure	69	64		
Any study drug-related TEAE	344	309		
Study drug-related TESAE	30	24		
Drug-related TEAE leading to dose modification	75	41		
Drug-related TEAE leading to stop of study drug	25	13		

Notes:

[8] - SAF: Number of Subjects Analyzed should be 652. Details refer to "End point description" above.

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Time to castration–resistant prostate cancer (CRPC) - Month

End point title	Time to castration–resistant prostate cancer (CRPC) - Month

End point description:

Time to castration-resistant prostate cancer was defined as the time from randomization to the first occurrence of one of the following events: PSA progression, Radiological progression by bone lesions, or Radiological progression by soft tissue and visceral lesions.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of an CRPC event up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[10]	654[11]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	19.1 (16.5 to 21.8)		

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

Statistical analysis title	CRPC - Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.302
upper limit	0.421

Notes:

[12] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).
[13] - One-sided p-value.

Secondary: Time to castration–resistant prostate cancer (CRPC) - Number of events

End point title	Time to castration–resistant prostate cancer (CRPC) - Number of events

End point description:

Time to castration-resistant prostate cancer was defined as the time from randomization to the first occurrence of one of the following events: PSA progression, Radiological progression by bone lesions, or Radiological progression by soft tissue and visceral lesions.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of an CRPC event up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[14]	654[15]		
Units: Subjects				
Number of subjects with event	225	391		
Number of subjects censored	426	263		

Notes:

[14] - FAS

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to pain progression - Month

End point title	Time to pain progression - Month

End point description:

Time to pain progression was defined as the time from randomization to the first date a patient experienced pain progression.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of a pain progression event up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[16]	654[17]		
Units: Months				
median (confidence interval 95%)	99999 (30.5 to 99999)	27.5 (22.0 to 36.1)		

Notes:

[16] - FAS

[17] - FAS

Statistical analyses

Statistical analysis title	Time to pain progression-Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0058 [19]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.792
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.95

Notes:

[18] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).
[19] - One-sided p-value.

Secondary: Time to pain progression - Number of events

End point title	Time to pain progression - Number of events

End point description:

Time to pain progression was defined as the time from randomization to the first date a patient experienced pain progression.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of a pain progression event up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[20]	654[21]		
Units: Subjects				
Number of subjects with event	222	248		
Number of subjects censored	429	406		

Notes:

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic skeletal event free survival (SSE–FS) - Number of events

End point title	Symptomatic skeletal event free survival (SSE–FS) - Number of events

End point description:

Symptomatic skeletal event-free survival (SSE-FS) was defined as the time from randomization to the first occurrence of an SSE or death from any cause, whichever occurred first.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event or death from any cause, whichever occurred first up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[22]	654[23]		
Units: Subjects				
Number of subjects with event	257	329		
Number of subjects censored	394	325		

Notes:

[22] - FAS

[23] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first symptomatic skeletal event (SSE) - Number of events

End point title	Time to first symptomatic skeletal event (SSE) - Number of events

End point description:

Time to the first SSE was defined as the time from randomization to the first occurrence of an SSE. Identical to the definition used for SSE-FS. Death was not considered as an event in this endpoint.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[24]	654[25]		
Units: Subjects				
Number (%) of subjects with event	95	108		
Number (%) of subjects censored	556	546		

Notes:

[24] - FAS

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic skeletal event free survival (SSE–FS) - Month

End point title	Symptomatic skeletal event free survival (SSE–FS) - Month

End point description:

Symptomatic skeletal event-free survival (SSE-FS) was defined as the time from randomization to the first occurrence of an SSE or death from any cause, whichever occurred first.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event or death from any cause, whichever occurred first up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[26]	654[27]		
Units: Months				
median (confidence interval 95%)	51.2 (47.2 to 99999)	39.7 (36.0 to 42.3)		

Notes:

[26] - FAS

[27] - FAS

Statistical analyses

Statistical analysis title	SSE–FS - Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001 [29]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.609
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.516
upper limit	0.718

Notes:

[28] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).
[29] - One-sided p-value.

Secondary: Time to initiation of subsequent antineoplastic therapy - Number of events

End point title	Time to initiation of subsequent antineoplastic therapy - Number of events

End point description:

Time to initiation of subsequent systemic antineoplastic therapy was defined as the time from randomization to the initiation of first subsequent systemic antineoplastic therapy.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the initiation of first subsequent systemic antineoplastic therapy up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[30]	654[31]		
Units: Subjects				
Number (%) of subjects with event	219	395		
Number (%) of subjects censored	432	259		

Notes:

[30] - FAS

[31] - FAS

Statistical analyses

No statistical analyses for this end point

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

End point title	Time to first symptomatic skeletal event (SSE) - Month

End point description:

Time to the first SSE was defined as the time from randomization to the first occurrence of an SSE. Identical to the definition used for SSE-FS. Death was not considered as an event in this endpoint.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first occurrence of an SSE event up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[32]	654[33]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[32] - FAS

[33] - FAS

Statistical analyses

Statistical analysis title	SSE - Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.0081 [35]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.712
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.539
upper limit	0.94

Notes:

[34] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).
[35] - One-sided p-value.

Secondary: Time to initiation of subsequent antineoplastic therapy - Month

End point title	Time to initiation of subsequent antineoplastic therapy - Month

End point description:

Time to initiation of subsequent systemic antineoplastic therapy was defined as the time from randomization to the initiation of first subsequent systemic antineoplastic therapy.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

End point type	Secondary

End point timeframe:

From randomization of the first subject to the initiation of first subsequent systemic antineoplastic therapy up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[36]	654[37]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	25.3 (23.1 to 28.8)		

Notes:

[36] - FAS

[37] - FAS

Statistical analyses

Statistical analysis title	Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	< 0.0001 [39]
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.388
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.328
upper limit	0.458

Notes:

[38] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).
[39] - One-sided p-value.

Secondary: Time to worsening of disease–related physical symptoms - Month

End point title	Time to worsening of disease–related physical symptoms - Month

End point description:

Time to worsening of disease-related physical symptoms was defined as the time from randomization to the first date a patient experienced an increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[40]	654[41]		
Units: Months				
median (confidence interval 95%)	19.3 (13.8 to 24.8)	19.4 (15.4 to 27.6)		

Notes:
[40] - FAS
[41] - FAS

Statistical analyses

Statistical analysis title	Worsening of disease - Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.7073 [43]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.894
upper limit	1.217

Notes:

[42] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).
[43] - One-sided p-value.

Secondary: Time to worsening of disease–related physical symptoms - Number of events

End point title	Time to worsening of disease–related physical symptoms - Number of events

End point description:

Time to worsening of disease-related physical symptoms was defined as the time from randomization to the first date a patient experienced an increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire.

Treatment period: treatment was provided for all patients, twice daily, until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[44]	654[45]		
Units: Subjects				
Number (%) of subjects with event	351	308		
Number (%) of subjects censored	300	346		

Notes:

[44] - FAS

[45] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to initiation of opioid use for ≥7 consecutive days - Number of events

End point title	Time to initiation of opioid use for ≥7 consecutive days - Number of events

End point description:

Time to the initiation of opioid use for ≥7 consecutive days was defined as the time fromrandomization to the date of the first opioid use for ≥7 consecutive days. Data of opioid use related to cancer pain was included in the analysis, and opioid use for non-malignant causes was excluded.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first opioid use for ≥7 consecutive days up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[46]	654[47]		
Units: Subjects				
Number of subjects with event	92	117		
Number of subjects censored	559	537		

Notes:

[46] - FAS

[47] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to initiation of opioid use for ≥7 consecutive days - Month

End point title	Time to initiation of opioid use for ≥7 consecutive days - Month

End point description:

Time to the initiation of opioid use for ≥7 consecutive days was defined as the time fromrandomization to the date of the first opioid use for ≥7 consecutive days. Data of opioid use related to cancer pain was included in the analysis, and opioid use for non-malignant causes was excluded.

Treatment period: until disease progression (symptomatic progressive disease, change of systemic antineoplastic therapy), unacceptable toxicity, consent withdrawal, withdrawal at the discretion of the investigator, death, or non-compliance.

Active follow-up visits from the discontinuation of the darolutamide or placebo treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data.

99999 = Value cannot be estimated due to censored data

End point type	Secondary

End point timeframe:

From randomization of the first subject to the first opioid use for ≥7 consecutive days up to 25 OCT 2021 cut-off date approximately 59 months

End point values	Darolutamide (BAY1841788) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651[48]	654[49]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[48] - FAS

[49] - FAS

Statistical analyses

Statistical analysis title	Initiation of opioid - Inferential statistics

Statistical analysis description:

One-sided p-value from log-rank test, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

Comparison groups	Darolutamide (BAY1841788) + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1305
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.0037 [51]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.688

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.523
upper limit	0.906

Notes:

[50] - Hazard ratio < 1 indicates superiority of Darolutamide+docetaxel arm over Placebo+docetaxel arm. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by EOD (Non-regional lymph nodes metastases only vs. Bone metastases with or without lymph node metastases vs. Visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP (<ULN vs. >=ULN).

[51] - One-sided p-value.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 30 days after the last administration, including adverse event of deaths (all causes) at any time during the study, up to cut-off date for the final completion analysis 11 APR 2023 (approximately 77 months).

Adverse event reporting additional description:

TEAEs were defined as any event arising or worsening after the first dose of darolutamide or placebo, until 30 days after the last dose of darolutamide or placebo administration.

Events causally related to treatment were considered as events causally related to either darolutamide/Docetaxel or Placebo/Docetaxel.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo + Docetaxel

Reporting group description:

Subjects received matching placebo to darolutamide in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started <=12 weeks before randomization.

Reporting group title	Darolutamide (BAY1841788) + Docetaxel

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 in addition to their standard treatment with docetaxel and androgen deprivation therapy (ADT). Docetaxel was administered for six cycles after randomization. The first cycle of docetaxel was administered within 6 weeks after start of study drug. ADT administration started <=12 weeks before randomization.

Serious adverse events	Placebo + Docetaxel	Darolutamide (BAY1841788) + Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	276 / 650 (42.46%)	306 / 652 (46.93%)	
number of deaths (all causes)	305	231	
number of deaths resulting from adverse events	26	29	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Medulloblastoma			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm malignant			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngeal cancer			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sebaceous carcinoma			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelofibrosis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phaeochromocytoma			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour pain			
subjects affected / exposed	2 / 650 (0.31%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	3 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Waldenstrom's macroglobulinaemia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 650 (0.15%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thyroid cancer			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral papilloma			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine adenocarcinoma			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic dissection			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematoma			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Spinal laminectomy			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardioversion			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia repair			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchidectomy			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilateral orchidectomy			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radical prostatectomy			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer surgery			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial appendage closure			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fusion surgery			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	15 / 650 (2.31%)	9 / 652 (1.38%)	
occurrences causally related to treatment / all	10 / 15	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	3 / 650 (0.46%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
General physical health deterioration			
subjects affected / exposed	4 / 650 (0.62%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 4	0 / 1	
Cardiac death			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Unevaluable event			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Loss of personal independence in daily activities			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic obstruction			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			

subjects affected / exposed	5 / 650 (0.77%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	4 / 6	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 650 (0.46%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	2 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 650 (0.62%)	6 / 652 (0.92%)	
occurrences causally related to treatment / all	3 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device deposit issue			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product contamination			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 650 (0.15%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 650 (1.23%)	6 / 652 (0.92%)	
occurrences causally related to treatment / all	6 / 10	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 650 (0.62%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	1 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy lymph gland			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			

subjects affected / exposed	10 / 650 (1.54%)	18 / 652 (2.76%)	
occurrences causally related to treatment / all	10 / 10	24 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	4 / 650 (0.62%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen abnormal			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaesthetic complication cardiac			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ankle fracture			
subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Snake bite			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post laminectomy syndrome			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Myocardial ischaemia			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 650 (0.31%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 650 (0.46%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Cardiac failure			

subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 650 (0.15%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus tachycardia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 650 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aphasia			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery thrombosis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar syndrome			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 650 (0.31%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 650 (0.31%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	7 / 650 (1.08%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 650 (0.77%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vagus nerve disorder			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal ganglia infarction			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 650 (0.62%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	39 / 650 (6.00%)	40 / 652 (6.13%)	
occurrences causally related to treatment / all	38 / 44	39 / 40	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulocytopenia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	14 / 650 (2.15%)	12 / 652 (1.84%)	
occurrences causally related to treatment / all	16 / 17	17 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow oedema syndrome			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 650 (0.15%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiretinal membrane			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastric ulcer			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal discomfort			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 650 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 650 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 650 (0.46%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal strangulation			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin mass			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	6 / 650 (0.92%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 650 (0.15%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urethral			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			

subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	4 / 650 (0.62%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Micturition disorder			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 650 (0.46%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	3 / 650 (0.46%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract pain			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder tamponade			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary fistula			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	6 / 650 (0.92%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	2 / 6	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 650 (0.15%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant urinary tract obstruction			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	3 / 650 (0.46%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	3 / 650 (0.46%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	6 / 650 (0.92%)	6 / 652 (0.92%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	6 / 650 (0.92%)	6 / 652 (0.92%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	3 / 650 (0.46%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 650 (0.15%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 650 (0.15%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubic pain			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 650 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	21 / 650 (3.23%)	16 / 652 (2.45%)	
occurrences causally related to treatment / all	5 / 22	8 / 17	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	2 / 650 (0.31%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	2 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 650 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyomyositis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 650 (0.92%)	6 / 652 (0.92%)	
occurrences causally related to treatment / all	2 / 6	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 650 (0.31%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sialoadenitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 650 (0.77%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 650 (1.08%)	7 / 652 (1.07%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 650 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
West Nile viral infection			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 650 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 650 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	3 / 650 (0.46%)	7 / 652 (1.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 4	
Arthritis infective			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetes mellitus			

subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 650 (0.46%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 650 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 650 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 650 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	3 / 650 (0.46%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperferritinaemia			
subjects affected / exposed	0 / 650 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 650 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Docetaxel	Darolutamide (BAY1841788) + Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	634 / 650 (97.54%)	636 / 652 (97.55%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	122 / 650 (18.77%)	128 / 652 (19.63%)	
occurrences (all)	136	141	

Hypertension			
subjects affected / exposed	61 / 650 (9.38%)	86 / 652 (13.19%)	
occurrences (all)	72	112	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	83 / 650 (12.77%)	84 / 652 (12.88%)	
occurrences (all)	110	104	
Pain			
subjects affected / exposed	42 / 650 (6.46%)	30 / 652 (4.60%)	
occurrences (all)	48	36	
Oedema peripheral			
subjects affected / exposed	169 / 650 (26.00%)	175 / 652 (26.84%)	
occurrences (all)	194	206	
Malaise			
subjects affected / exposed	67 / 650 (10.31%)	58 / 652 (8.90%)	
occurrences (all)	97	78	
Fatigue			
subjects affected / exposed	215 / 650 (33.08%)	222 / 652 (34.05%)	
occurrences (all)	287	291	
Asthenia			
subjects affected / exposed	65 / 650 (10.00%)	71 / 652 (10.89%)	
occurrences (all)	83	89	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	34 / 650 (5.23%)	38 / 652 (5.83%)	
occurrences (all)	38	50	
Dyspnoea			
subjects affected / exposed	71 / 650 (10.92%)	62 / 652 (9.51%)	
occurrences (all)	78	73	
Cough			
subjects affected / exposed	73 / 650 (11.23%)	87 / 652 (13.34%)	
occurrences (all)	83	103	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	80 / 650 (12.31%)	77 / 652 (11.81%)	
occurrences (all)	93	85	

Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	43 / 650 (6.62%)	45 / 652 (6.90%)	
occurrences (all)	53	53	
White blood cell count decreased			
subjects affected / exposed	142 / 650 (21.85%)	155 / 652 (23.77%)	
occurrences (all)	360	395	
Weight increased			
subjects affected / exposed	105 / 650 (16.15%)	116 / 652 (17.79%)	
occurrences (all)	130	147	
Weight decreased			
subjects affected / exposed	37 / 650 (5.69%)	27 / 652 (4.14%)	
occurrences (all)	37	32	
Neutrophil count decreased			
subjects affected / exposed	151 / 650 (23.23%)	165 / 652 (25.31%)	
occurrences (all)	415	432	
Aspartate aminotransferase increased			
subjects affected / exposed	66 / 650 (10.15%)	87 / 652 (13.34%)	
occurrences (all)	84	120	
Alanine aminotransferase increased			
subjects affected / exposed	81 / 650 (12.46%)	99 / 652 (15.18%)	
occurrences (all)	103	132	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	33 / 650 (5.08%)	45 / 652 (6.90%)	
occurrences (all)	37	64	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	68 / 650 (10.46%)	65 / 652 (9.97%)	
occurrences (all)	72	74	
Paraesthesia			
subjects affected / exposed	55 / 650 (8.46%)	42 / 652 (6.44%)	
occurrences (all)	66	45	
Neuropathy peripheral			
subjects affected / exposed	68 / 650 (10.46%)	77 / 652 (11.81%)	
occurrences (all)	72	91	

Hypoaesthesia			
subjects affected / exposed	29 / 650 (4.46%)	38 / 652 (5.83%)	
occurrences (all)	40	44	
Headache			
subjects affected / exposed	49 / 650 (7.54%)	59 / 652 (9.05%)	
occurrences (all)	58	72	
Dysgeusia			
subjects affected / exposed	80 / 650 (12.31%)	71 / 652 (10.89%)	
occurrences (all)	84	88	
Dizziness			
subjects affected / exposed	52 / 650 (8.00%)	60 / 652 (9.20%)	
occurrences (all)	64	69	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	164 / 650 (25.23%)	185 / 652 (28.37%)	
occurrences (all)	227	276	
Neutropenia			
subjects affected / exposed	67 / 650 (10.31%)	62 / 652 (9.51%)	
occurrences (all)	103	108	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	43 / 650 (6.62%)	38 / 652 (5.83%)	
occurrences (all)	47	40	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	58 / 650 (8.92%)	53 / 652 (8.13%)	
occurrences (all)	69	63	
Stomatitis			
subjects affected / exposed	57 / 650 (8.77%)	67 / 652 (10.28%)	
occurrences (all)	69	87	
Nausea			
subjects affected / exposed	134 / 650 (20.62%)	117 / 652 (17.94%)	
occurrences (all)	174	150	
Diarrhoea			
subjects affected / exposed	157 / 650 (24.15%)	168 / 652 (25.77%)	
occurrences (all)	225	229	
Constipation			

subjects affected / exposed	132 / 650 (20.31%)	149 / 652 (22.85%)	
occurrences (all)	162	202	
Abdominal pain			
subjects affected / exposed	37 / 650 (5.69%)	36 / 652 (5.52%)	
occurrences (all)	40	40	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	45 / 650 (6.92%)	53 / 652 (8.13%)	
occurrences (all)	58	64	
Nail discolouration			
subjects affected / exposed	52 / 650 (8.00%)	50 / 652 (7.67%)	
occurrences (all)	52	51	
Dry skin			
subjects affected / exposed	35 / 650 (5.38%)	48 / 652 (7.36%)	
occurrences (all)	37	54	
Alopecia			
subjects affected / exposed	264 / 650 (40.62%)	267 / 652 (40.95%)	
occurrences (all)	265	268	
Pruritus			
subjects affected / exposed	52 / 650 (8.00%)	46 / 652 (7.06%)	
occurrences (all)	62	54	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	43 / 650 (6.62%)	31 / 652 (4.75%)	
occurrences (all)	47	33	
Haematuria			
subjects affected / exposed	36 / 650 (5.54%)	59 / 652 (9.05%)	
occurrences (all)	43	73	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	78 / 650 (12.00%)	104 / 652 (15.95%)	
occurrences (all)	95	148	
Myalgia			
subjects affected / exposed	65 / 650 (10.00%)	74 / 652 (11.35%)	
occurrences (all)	84	103	
Muscular weakness			

subjects affected / exposed	48 / 650 (7.38%)	51 / 652 (7.82%)	
occurrences (all)	54	59	
Bone pain			
subjects affected / exposed	82 / 650 (12.62%)	80 / 652 (12.27%)	
occurrences (all)	96	91	
Back pain			
subjects affected / exposed	121 / 650 (18.62%)	128 / 652 (19.63%)	
occurrences (all)	147	154	
Arthralgia			
subjects affected / exposed	173 / 650 (26.62%)	186 / 652 (28.53%)	
occurrences (all)	249	270	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	63 / 650 (9.69%)	57 / 652 (8.74%)	
occurrences (all)	92	91	
Upper respiratory tract infection			
subjects affected / exposed	46 / 650 (7.08%)	57 / 652 (8.74%)	
occurrences (all)	52	73	
Nasopharyngitis			
subjects affected / exposed	46 / 650 (7.08%)	46 / 652 (7.06%)	
occurrences (all)	56	69	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	86 / 650 (13.23%)	121 / 652 (18.56%)	
occurrences (all)	96	157	
Hyperglycaemia			
subjects affected / exposed	61 / 650 (9.38%)	77 / 652 (11.81%)	
occurrences (all)	74	100	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2016	Protocol Amendment 1, dated 20 SEP 2016, was valid only for centers located in China. The main modification was: • Addition of new China specific pharmacokinetic (PK) sub-study
04 October 2016	Protocol Amendment 2, dated 04 OCT 2016, was globally implemented. The main modifications were: • New drug-drug interaction data added • Clarification of PK analysis o Patients participating to the detailed PK analysis (dense PK sampling) had received at least one cycle of docetaxel o Clarified the timing of the sparse PK sampling o Additional analysis of docetaxel in all the randomized patients • Addition of non-protein-bound (free) testosterone analysis
04 November 2016	Protocol Amendment 3, dated 04 NOV 2016, was valid only for centers located in UK. The main modification was: • List of acceptable effective contraception methods to be used was added by request of the Medicines and Healthcare Products Regulatory Agency (MHRA)
31 January 2017	Protocol Amendment 4, dated 31 JAN 2017, was valid only for centers located in Japan. The main modification was: • Added reporting requirements for medical device failures for imported and non-approved third-party devices used in Bayer-sponsored clinical trials in Japan to the PMDA, IECs/IRBs and investigators
12 February 2018	Protocol Amendment 5, dated 12 FEB 2018, was globally implemented. The main modifications were: • New drug-drug interaction data added • Modification of the dosing language to align darolutamide dosing wording across the development program • Clarification of docetaxel dosage and administration in accordance with the label and clarified that the first cycle of docetaxel should be administered within 6 weeks after start of study drug instead of 6 weeks after randomization • Guidance on laboratory tests before each docetaxel cycle to be in line with docetaxel label requirements • Clarification added for the evaluation of soft tissue and visceral lesions; these were to be performed using the same radiological methods and assessed by RECIST criteria • ADT switch to LHRH agonist was added to the list of prohibited concomitant medications and treatments and a clarification was added to allow an ADT switch to an antagonist during study treatment • Collection of whole blood sample for pharmacogenetics test allowed at other visits if missed at Visit 1 • Clarification added for: o Unblinding in non–emergency situations was not permitted o For PK sampling o For laboratory safety assessments

10 December 2019	Protocol Amendment 6, dated 10 DEC 2019, was globally implemented. The main modifications were: • Option to continue darolutamide treatment in a separate program was added for those patients who are ongoing on darolutamide treatment; patients assigned to placebo would discontinue treatment and complete the study • Additional survival sweeps were added • Detailed information on darolutamide drug-drug interactions was removed and information on the effect of darolutamide on the PK of docetaxel was updated • Guidance and cautions for specific drug-drug interactions were removed based on new data on these interactions becoming available • AE reporting was modified to clarify that disease progression should not be reported as an AE; only the associated signs and symptoms should be reported as AEs • In a subset of patients, additional determination of total and free testosterone was added to be performed also at the EOT Visit
26 May 2020	Protocol Amendment 7, dated 26 MAY 2020, was globally implemented. The main modifications were: • Planned second interim analysis was removed due to the implications of the COVID–19 pandemic on the conduct of study procedures and data collection at the study sites. The risk for not achieving the needed quality of data for a formal analysis at that point in time was considered to be too high • Clarification added for biomarker analysis and reporting • Added text regarding ranking of secondary endpoints • Due to removal of interim analysis 2, the sentence regarding alpha–spending was removed and a statement about beta–spending was added for clarification
30 August 2021	Protocol Amendment 8, dated 30 AUG 2021 was valid only for centers located in Japan. The main modifications were: • To minimize the burden for subjects still enrolled after the study reached primary completion, the number of procedures will be reduced to a minimum, to guarantee patient treatment continuation and safety • Japanese subjects will be provided the opportunity to continue treatment at the discretion of the investigator
02 August 2022	Protocol Amendment 9, dated 02 AUG 2022 was valid only for centers located in Japan. However, it was prepared as a consolidated protocol and therefore also includes the latest global protocol version 5.0 (amendment 7). It provided guidance on the criteria for study drug discontinuation in the event of a suspected drug-induced liver injury (DILI) because of newly identified safety data across darolutamide clinical trials, including cases of idiosyncratic hepatic reactions that were reversible upon treatment discontinuation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported