Clinical trial results:
A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Chemotherapy Naïve Metastatic Castration-Resistant Prostate Cancer

Summary

EudraCT number	2010-018661-35
Trial protocol	FR HU EE BE SK LV FI NL ES LT CZ AT GB PT SE IE DE PL IT BG GR RO
Global end of trial date	07 April 2016

Results information

Result version number	v1 (current)
This version publication date	23 April 2017
First version publication date	23 April 2017

Trial information

Trial identification

Sponsor protocol code	C21004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01193244
WHO universal trial number (UTN)	U1111-1181-0387

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	40 Landsdowne Street, Cambridge, MA, United States, 02139
Public contact	Study Manager, Millennium Medical and Drug Information Center, 001 866-835-2233, trialdisclosures@takeda.com
Scientific contact	Study Manager, Millennium Medical and Drug Information Center, 001 866-835-2233, trialdisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to determine if orteronel plus prednisone improved radiographic progression-free survival (rPFS) and to determine if orteronel plus prednisone improved overall survival (OS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 44
Country: Number of subjects enrolled	United States: 295
Country: Number of subjects enrolled	Austria: 24
Country: Number of subjects enrolled	Belarus: 16
Country: Number of subjects enrolled	Belgium: 39
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Czech Republic: 31
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	Estonia: 6
Country: Number of subjects enrolled	France: 121
Country: Number of subjects enrolled	Germany: 69
Country: Number of subjects enrolled	Greece: 39
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Ireland: 24
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Latvia: 26
Country: Number of subjects enrolled	Lithuania: 37
Country: Number of subjects enrolled	Netherlands: 73

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Slovakia: 20
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Switzerland: 18
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	United Kingdom: 95
Country: Number of subjects enrolled	Australia: 54
Country: Number of subjects enrolled	Brazil: 91
Country: Number of subjects enrolled	Chile: 40
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	New Zealand: 51
Country: Number of subjects enrolled	Peru: 16
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	1560
EEA total number of subjects	748

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)	354
From 65 to 84 years	1144
85 years and over	62

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 324 investigative sites in North America, Europe, Australia, Brazil, Chile, Colombia, Hong Kong, Peru, Puerto Rico, Israel, Japan, Mexico, New Zealand, Singapore, South Africa, and Taiwan from 19 October 2010 to 7 April 2016.

Pre-assignment

Screening details:

Subjects who were chemotherapy-naïve, had metastatic castration-resistant prostate cancer (mCRPC) with documented progressive metastatic disease were enrolled to receive: Orteronel 400 milligram (mg) + Prednisone 5 mg or Placebo + Prednisone 5 mg. After unblinding, 7 subjects who received placebo crossed over to receive Orteronel.

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, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Prednisone 5 mg

Arm description:

Orteronel placebo-matching tablets, orally, twice daily (BID) and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

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

Dosage and administration details:

Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

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

Dosage and administration details:

Orteronel placebo-matching tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

Arm title	Orteronel 400 mg + Prednisone 5 mg

Arm description:

Orteronel 400 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study. In Japan, subjects were administered with Orteronel 300 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

Arm type	Experimental

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

Investigational medicinal product name	Orteronel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Orteronel 400 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study. In Japan, subjects were administered with Orteronel 300 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

Number of subjects in period 1	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg
Started	779	781
Completed	391	391
Not completed	388	390
Consent withdrawn by subject	79	97
Other	303	278
Lost to follow-up	6	15

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Prednisone 5 mg
Reporting group description:	
Orteronel placebo-matching tablets, orally, twice daily (BID) and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.	
Reporting group title	Orteronel 400 mg + Prednisone 5 mg
Reporting group description:	
Orteronel 400 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study. In Japan, subjects were administered with Orteronel 300 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.	

Reporting group values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg	Total
Number of subjects	779	781	1560
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	176	178	354
From 65-84 years	573	571	1144
85 years and over	30	32	62
Age Continuous Units: years			
arithmetic mean	71.1	70.9	
standard deviation	± 8.19	± 8.26	-
Gender, Male/Female Units: Subjects			
Female	0	0	0
Male	779	781	1560
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	10	12	22
Asian	51	38	89
Native Hawaiian or Other Pacific Islander	2	1	3
Black or African American	19	25	44
White	670	685	1355
Unknown or Not Reported	12	3	15
Other	15	17	32
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	90	107	197
Not Hispanic or Latino	672	669	1341

Unknown or Not Reported	17	5	22
Region of Enrollment Units: Subjects			
Canada	22	22	44
United States	147	148	295
Austria	12	12	24
Belarus	6	10	16
Belgium	18	21	39
Bulgaria	6	6	12
Croatia	5	1	6
Czech Republic	13	18	31
Estonia	2	4	6
Finland	9	4	13
France	66	55	121
Germany	29	40	69
Greece	23	16	39
Hungary	3	4	7
Ireland	11	13	24
Italy	10	8	18
Latvia	12	14	26
Lithuania	19	18	37
Netherlands	35	38	73
Poland	0	4	4
Portugal	4	4	8
Romania	20	13	33
Slovakia	9	11	20
Spain	14	12	26
Sweden	11	6	17
Switzerland	10	8	18
Ukraine	25	23	48
United Kingdom	42	53	95
Australia	27	27	54
Brazil	41	50	91
Chile	20	20	40
Colombia	3	6	9
Hong Kong	1	3	4
Israel	14	4	18
Japan	22	18	40
Mexico	7	9	16
New Zealand	25	26	51
Peru	6	10	16
Puerto Rico	1	1	2
Singapore	5	2	7
South Africa	6	4	10
Taiwan, Province Of China	12	10	22
Russia	6	5	11
Study Specific Characteristic | Height			
Height data was available for 1558 subjects as follows: n= 778, 780.			
Units: centimeter			
arithmetic mean	172.77	173.26	
standard deviation	± 7.485	± 7.858	-
Study Specific Characteristic | Weight			

Weight data was available for 1559 subjects as follows: n= 778, 781.			
Units: kilogram			
arithmetic mean	84.04	85.09	
standard deviation	± 15.846	± 16.286	-
Study Specific Characteristic | Body Mass Index (BMI)			
BMI data was available for 1557 subjects as follows: n= 777, 780.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	28.09	28.28	
standard deviation	± 4.651	± 4.73	-

End points

End points reporting groups

Reporting group title	Placebo + Prednisone 5 mg
Reporting group description:	
Orteronel placebo-matching tablets, orally, twice daily (BID) and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.	
Reporting group title	Orteronel 400 mg + Prednisone 5 mg
Reporting group description:	
Orteronel 400 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study. In Japan, subjects were administered with Orteronel 300 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.	
Subject analysis set title	Orteronel 400 mg + Prednisone 5 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Orteronel 400 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study. In Japan, subjects were administered with Orteronel 300 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.	

Primary: Radiographic Progression-free Survival (rPFS)

End point title	Radiographic Progression-free Survival (rPFS)
End point description:	
rPFS was defined as the time from randomization to the first objective evidence of radiographic disease progression assessed by independent central radiology review or death due to any cause, whichever occurred first. Radiographic disease progression was evaluated by computerized tomography (CT) scan or magnetic resonance imaging (MRI) and radionuclide bone scans at regularly scheduled visits. Radiographic disease progression in bone required a confirmatory scan. Radiographic disease progression in soft tissue did not require a confirmatory scan for purposes of analysis. Radiographic disease progression was evaluated by independent central radiology review using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 for soft tissue disease and Prostate Cancer Working Group (PCWG2) guidelines for bone disease. Subjects who did not reach the endpoint were censored at their last assessment. Intent-to-treat (ITT) population included all subjects who were randomized.	
End point type	Primary
End point timeframe:	
Baseline until radiographic disease progression or death, whichever occurred first (approximately up to 4.7 years)	

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	8.7 (8.32 to 10.91)	13.8 (13.05 to 14.92)		

Statistical analyses

Statistical analysis title	Orteronel vs Placebo

Statistical analysis description:

Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors of region and radiographic disease progression at baseline with treatment as a factor in the model. A hazard ratio less than (<) 1 indicated better prevention of death in the orteronel group compared to the placebo group. From log-rank test stratified by region and radiographic disease progression at Baseline.

Comparison groups	Placebo + Prednisone 5 mg v Orteronel 400 mg + Prednisone 5 mg
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.707
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.626
upper limit	0.799

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was calculated from the date of subject randomization to the date of subject death due to any cause. Subjects without documentation of death at time of the analysis were censored as of the date the subject was last known to be alive, or the data cutoff date, whichever was earlier. ITT population included all subjects who were randomized.

End point type	Primary

End point timeframe:

Baseline until death (up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	29.5 (27.28 to 32.38)	29.9 (27.88 to 33.04)		

Statistical analyses

Statistical analysis title	Orteronel vs Placebo

Statistical analysis description:

Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors of region and radiographic disease progression at baseline with treatment as a factor in the model. A hazard ratio <1 indicated better prevention of death in the orteronel group compared to the placebo group. From log-rank test stratified by region and radiographic disease progression at baseline.

Comparison groups	Placebo + Prednisone 5 mg v Orteronel 400 mg + Prednisone 5 mg
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59755
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.963
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.838
upper limit	1.107

Secondary: Percentage of Subjects Achieving 50 Percent Reduction From Baseline in Prostate Specific Antigen (PSA50) Response at Week 12

End point title	Percentage of Subjects Achieving 50 Percent Reduction From Baseline in Prostate Specific Antigen (PSA50) Response at Week 12

End point description:

The PSA50 is defined as a decline of at least 50 percent (%) from baseline. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: percentage of subjects				
number (confidence interval 95%)	24.6 (21.7 to 27.8)	42.6 (39.1 to 46.2)		

Statistical analyses

Statistical analysis title	Orteronel vs Placebo

Statistical analysis description:

Logistic regression model with prognostic factors: region; radiographic disease progression at baseline; age; race; baseline Eastern Cooperative Oncology Group (ECOG) score; Gleason score at initial

diagnosis; baseline PSA, natural log scale; presence of visceral disease; alkaline phosphatase; lactate dehydrogenase; and hemoglobin. Odds ratio greater than (>)1 favored orteronel. P-values tested for odds ratio equal to 1.

Comparison groups	Placebo + Prednisone 5 mg v Orteronel 400 mg + Prednisone 5 mg
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.724
upper limit	2.721

Secondary: Percentage of Subjects With Favorable Circulating Tumor Cell Count (CTC) Levels at Week 12

End point title	Percentage of Subjects With Favorable Circulating Tumor Cell Count (CTC) Levels at Week 12

End point description:

A favorable CTC count was defined as <5 counts per 7.5 milliliter (mL) in whole blood. An unfavorable CTC count was defined as greater than or equal to (>=) 5 counts/7.5 mL in whole blood. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: percentage of subjects				
number (confidence interval 95%)	9.1 (7.2 to 11.4)	15.4 (12.9 to 18.1)		

Statistical analyses

Statistical analysis title	Orteronel vs Placebo

Statistical analysis description:

Logistic regression model with prognostic factors: region; radiographic disease progression at baseline; age; race; baseline ECOG score; Gleason score at initial diagnosis; baseline PSA, natural log scale; presence of visceral disease; alkaline phosphatase; lactate dehydrogenase; and hemoglobin. Odds ratio > 1 favored orteronel. P-values tested for odds ratio equal to 1.

Comparison groups	Placebo + Prednisone 5 mg v Orteronel 400 mg + Prednisone 5 mg
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.712
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.235
upper limit	2.373

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

Time to pain progression defined as time from subject randomization to first assessment date of pain progression. Pain progression defined as occurrence of 1 of the following, confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later: The brief pain inventory-short form(BPI-SF) worst pain score>=4 with a >=2 point increase over baseline in BPI-SF worst pain score with stable/increased analgesic use; The BPI-SF worst pain score>=4 but not less than baseline with new/increased (relative to baseline) Step II or Step III analgesic use; The BPI-SF worst pain score<=3 but not less than baseline with new/increased (relative to baseline) Step III analgesic use. BPI-SF(11-item questionnaire), designed to assess severity and impact of pain on daily functions. Total score ranged from 0 to 100; lower scores indicative of less pain. ITT population. Here, 99999 in median and confidence interval (CI) signifies "not estimable due to low number of events in arm".

End point type	Secondary

End point timeframe:

Baseline until End of treatment (EOT) (approximately up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (28.57 to 99999)		

Statistical analyses

Statistical analysis title	Orteronel vs Placebo

Statistical analysis description:

Hazard ratio is based on a stratified Cox’s proportional hazard regression model with stratification factors of region and radiographic disease progression at baseline with treatment as a factor in the

model. A hazard ratio <1 indicated better prevention of death in the orteronel group compared to the placebo group. From log-rank test stratified by region and radiographic disease progression at baseline.

Comparison groups	Placebo + Prednisone 5 mg v Orteronel 400 mg + Prednisone 5 mg
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33906
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.885
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.688
upper limit	1.138

Secondary: Number of Subjects Reporting one or More Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects Reporting one or More Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 61 Day 58)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be analysed in safety analysis set. Orteronel 400 mg + Prednisone 5 mg safety analysis set included subjects who received placebo crossed over to receive Orteronel after unblinding.

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	770	784		
Units: subjects				
TEAE	733	769		
Serious Adverse Events (SAE)	321	380		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events Greater Than or Equal to (>=) Grade 3

End point title	Number of Subjects With Treatment-emergent Adverse Events Greater Than or Equal to (>=) Grade 3[2]

End point description:

Grade 3 (Severe) events=unacceptable or intolerable events, significantly interrupting usual daily activity, require systemic drug therapy/other treatment. Grade 4 (Life-threatening) events caused subject to be in imminent danger of death. Grade 5 (Death) events=death related to an AE. Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 61 Day 58)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Endpoint was planned to be analysed in safety analysis set. Orteronel 400 mg + Prednisone 5 mg safety analysis set included subjects who received placebo crossed over to receive Orteronel after unblinding.

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	770	784		
Units: subjects				
Grade 3 or higher TEAE	405	537		
Grade 5 (Death)	78	77		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With TEAEs Related to Vital Signs

End point title	Number of Subjects With TEAEs Related to Vital Signs[3]

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 61 Day 58)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Endpoint was planned to be analysed in safety analysis set. Orteronel 400 mg + Prednisone 5 mg safety analysis set included subjects who received placebo crossed over to receive Orteronel after unblinding.

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	770	784		
Units: subjects				
Hypertension	76	98		
Pyrexia	26	41		

Hypotension	12	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With TEAEs Related to Weight

End point title	Number of Subjects With TEAEs Related to Weight[4]

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (Cycle 61 Day 58)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be analysed in safety analysis set. Orteronel 400 mg + Prednisone 5 mg safety analysis set included subjects who received placebo crossed over to receive Orteronel after unblinding.

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	770	784		
Units: subjects				
Weight decreased	47	119		
Weight increased	36	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worst Change From Baseline in Eastern Co-operative Oncology Group (ECOG) Performance Status

End point title	Number of Subjects With Worst Change From Baseline in Eastern Co-operative Oncology Group (ECOG) Performance Status

End point description:

ECOG assessed subject's performance status on 5 point scale: 0=Fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, ambulatory/able to carry out light or sedentary work; 2=ambulatory (>50 percent of waking hours [hrs]), capable of all self care, unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50 percent of waking hrs; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead. Worst change was defined as the worst overall change that occurred in ECOG status at any measured time point during the treatment period. Safety population where baseline and post-baseline assessments were available. Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline until EOT (approximately up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	760	771		
Units: subjects				
Baseline: 0; Overall: 0	251	200		
Baseline: 0; Overall: 1	177	237		
Baseline: 0; Overall: 2	47	66		
Baseline: 0; Overall: 3	22	15		
Baseline: 0; Overall: 4	7	7		
Baseline: 1; Overall: 0	6	6		
Baseline: 1; Overall: 1	162	147		
Baseline: 1; Overall: 2	57	60		
Baseline: 1; Overall: 3	28	26		
Baseline: 1; Overall: 4	2	6		
Baseline: 2; Overall: 2	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Findings

End point title	Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Findings[5]

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline up to EOT (Cycle 61 Day 58)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be analysed in safety analysis set. Orteronel 400 mg + Prednisone 5 mg safety analysis set included subjects who received placebo crossed over to receive Orteronel after unblinding.

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	770	784		
Units: subjects	130	163		

Statistical analyses

No statistical analyses for this end point

Secondary: Worst Change From Baseline Over Time in Cardiac Ejection Fraction

End point title	Worst Change From Baseline Over Time in Cardiac Ejection Fraction

End point description:

Worst change was defined as the worst overall change that occurred in cardiac ejection fraction at any measured time point. Safety population where baseline and post-baseline assessments were available. Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline up to 30 days or EOT whichever is later (approximately up to Cycle 61 Day 58)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	676	670		
Units: percent ejection fraction				
arithmetic mean (standard deviation)	-3.8 (± 6.93)	-4.8 (± 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With TEAEs Categorized Into Investigations Related to Chemistry, Hematology or Coagulation

End point title	Number of Subjects With TEAEs Categorized Into Investigations Related to Chemistry, Hematology or Coagulation[6]

End point description:

Safety population included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Baseline up to 30 days or EOT whichever is later (approximately up to Cycle 61 Day 58)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be analysed in safety analysis set. Orteronel 400 mg + Prednisone 5 mg safety analysis set included subjects who received placebo crossed over to receive Orteronel after unblinding.

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	770	784		
Units: subjects				
Investigations	215	399		
Blood and lymphatic system disorders	114	107		
Metabolism and nutrition disorders	204	336		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Skeletal Related Events (SRE)

End point title	Percentage of Subjects With Skeletal Related Events (SRE)

End point description:

Skeletal related (SRE) event is defined as a fracture or spinal cord compression or the need for radiation or surgery at the site of a prostate cancer metastatic lesion that is substantiated by radiographic or pathologic evidence. The ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline up to EOT (approximately up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: percentage of subjects				
number (confidence interval 95%)	10.9 (8.8 to 13.3)	8.6 (6.7 to 10.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to SRE

End point title	Time to SRE

End point description:

Time to SRE is defined as the time from randomization to SRE, or death due to any cause, whichever comes first. SRE is defined as a fracture or spinal cord compression or the need for radiation or surgery at the site of a prostate cancer metastatic lesion that is substantiated by radiographic or pathologic evidence. The ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline up to EOT (Cycle 61 Day 58)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	9 (8.32 to 10.98)	13.9 (13.68 to 16.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving PSA50 Response at any Time During the Study

End point title	Percentage of Subjects Achieving PSA50 Response at any Time During the Study

End point description:

The PSA50 is defined as a decline of PSA by 50 percent from baseline. ITT population where baseline and post-baseline assessments were available. The ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Cycle: 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34 and 37

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: percentage of subjects				
number (confidence interval 95%)				
Cycle 4 (n= 687, 672)	28.09 (24.76 to 31.62)	49.7 (45.86 to 53.55)		
Cycle 7 (n= 541, 540)	34.94 (30.92 to 39.12)	54.81 (50.51 to 59.07)		

Cycle 10 (n= 438, 450)	36.99 (32.45 to 41.7)	56 (51.28 to 60.64)		
Cycle 13 (n= 344, 382)	37.21 (32.09 to 42.56)	53.14 (48 to 58.24)		
Cycle 16 (n= 286, 303)	34.27 (28.78 to 40.08)	54.13 (48.33 to 59.84)		
Cycle 19 (n= 228, 272)	37.72 (31.41 to 44.36)	52.94 (46.82 to 59)		
Cycle 22 (n= 184, 211)	33.15 (26.4 to 40.46)	54.03 (47.05 to 60.89)		
Cycle 25 (n= 109, 119)	35.78 (26.83 to 45.53)	46.22 (37.04 to 55.59)		
Cycle 28 (n= 67, 77)	44.78 (32.6 to 57.42)	48.05 (36.52 to 59.74)		
Cycle 31 (n= 35, 39)	34.29 (19.13 to 52.21)	48.72 (32.42 to 65.22)		
Cycle 34 (n= 22, 18)	36.36 (17.2 to 59.34)	38.89 (17.3 to 64.25)		
Cycle 37 (n= 7, 5)	71.43 (29.04 to 96.33)	40 (5.27 to 85.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving 90 Percent Reduction From Baseline in Prostate Specific Antigen (PSA90 Response) at Week 12

End point title	Percentage of Subjects Achieving 90 Percent Reduction From Baseline in Prostate Specific Antigen (PSA90 Response) at Week 12

End point description:

The PSA90 is defined as a decline of PSA by 90 percent from baseline. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: percentage of subjects				
number (not applicable)	5.4	16.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving PSA90 Response at any Time During the Study

End point title	Percentage of Subjects Achieving PSA90 Response at any Time During the Study

End point description:

The PSA90 is defined as a decline of PSA by 90 percent from baseline. ITT population where baseline and post-baseline assessments were available. The ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Cycle: 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34 and 37

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: percentage of subjects				
number (confidence interval 95%)				
Cycle 4 (n= 687, 672)	5.39 (3.82 to 7.35)	16.67 (13.93 to 19.7)		
Cycle 7 (n= 541, 540)	8.69 (6.45 to 11.39)	22.22 (18.78 to 25.97)		
Cycle 10 (n= 438, 450)	11.64 (8.79 to 15.02)	26.44 (22.42 to 30.78)		
Cycle 13 (n= 344, 382)	12.79 (9.45 to 16.79)	26.18 (21.84 to 30.89)		
Cycle 16 (n= 286, 303)	12.24 (8.67 to 16.61)	25.74 (20.91 to 31.05)		
Cycle 19 (n= 228, 272)	12.72 (8.69 to 17.75)	26.1 (20.99 to 31.75)		
Cycle 22 (n= 184, 211)	10.87 (6.77 to 16.29)	28.44 (22.45 to 35.03)		
Cycle 25 (n= 109, 119)	11.01 (5.82 to 18.44)	21.01 (14.08 to 29.43)		
Cycle 28 (n= 67, 77)	16.42 (8.49 to 27.48)	27.27 (17.74 to 38.62)		
Cycle 31 (n= 35, 39)	8.57 (1.8 to 23.06)	12.82 (4.3 to 27.43)		
Cycle 34 (n= 22, 18)	4.55 (0.12 to 22.84)	22.22 (6.41 to 47.64)		
Cycle 37 (n= 7, 5)	14.29 (0.36 to 57.87)	20 (0.51 to 71.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA Progression

End point title	Time to PSA Progression

End point description:

Time to PSA progression was defined as time from randomization to a PSA increase of 25 percent and PSA rise of at least 2 nanogram per milliliter (ng/mL) above the lowest value observed post baseline or, if no PSA decline occurred post baseline, compared to baseline PSA.

End point type	Secondary

End point timeframe:

Baseline until the final on treatment assessment or until end of short term follow-up following discontinuation of treatment, whichever occurred later (approximately up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	5.59 (5.56 to 5.59)	8.3 (8.28 to 8.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Docetaxel Chemotherapy

End point title	Time to Docetaxel Chemotherapy

End point description:

Time to docetaxel based chemotherapy is defined as the time from randomization to the start of docetaxel based chemotherapy for prostate cancer, regardless of whether the subject received concurrent orteronel or not. Deaths due to disease progression prior to Docetaxel based chemotherapy were considered as events. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline until start of docetaxel chemotherapy (up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	19 (16.44 to 21.43)	23 (20.71 to 24.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Subsequent Antineoplastic Therapy

End point title	Time to Subsequent Antineoplastic Therapy

End point description:

Time to subsequent antineoplastic therapy is defined as the time from randomization to the start of any alternate antineoplastic therapy for prostate cancer. Deaths due to disease progression prior to antineoplastic therapy for prostate cancer are considered as events. Otherwise, time to next therapy is censored at the date of death or the last date the subject was known to be alive or the data cutoff date, whichever is earlier. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline until start of subsequent antineoplastic therapy (up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	13.9 (12.16 to 14.86)	17.2 (15.09 to 18.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Objective Response

End point title	Percentage of Subjects With Objective Response

End point description:

Percentage of subjects with objective response based assessment of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST 1.1. A CR was defined as the disappearance of all target lesions determined by computerized tomography (CT) or MRI. Any pathological lymph nodes (whether target or non-target) must have had reduction in short axis to <10 millimetre (mm). A PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of longest diameters of non-lymph node lesions and of the short diameter or short axis of lymph nodes. The Response Evaluation Criteria in Solid Tumors (RECIST) evaluable population included all subjects who had measurable disease by RECIST 1.1 at the baseline assessment.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death, whichever occurred first (approximately up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	236		
Units: percentage of subjects				
number (confidence interval 95%)	15.2 (11 to 20.4)	34.7 (28.7 to 41.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration in Global Health Status

End point title	Time to Deterioration in Global Health Status

End point description:

Global health status deterioration is defined as a drop greater than 16 points from the baseline assessment, confirmed at least 3 weeks later, on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30 (EORTC QLQ-C30) index after the score has been linearly transformed to a 0 to 100 scale. EORTC QLQ-C30 consists of 30 questions, where question 1 to 28 can be answered with 1: Not at all, 2: A little, 3: Quite a bit, 4: Very much and question 29 to 30 with 1: Very poor to 7: Excellent. For subscales a high score from 0-100 indicates: high global quality of life, high level of functioning (physical, role, emotional, cognitive, social) or a high level of symptoms (fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties).

End point type	Secondary

End point timeframe:

Baseline until EOT (approximately up to 4.7 years)

End point values	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: months				
median (confidence interval 95%)	10.7 (8.97 to 11.11)	8.3 (7.36 to 10.16)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of study drug and no more than 30 days after the last dose of study drug (up to Cycle 61 Day 58).

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo + Prednisone 5 mg

Reporting group description:

Orteronel placebo-matching tablets, orally, twice daily (BID) and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

Reporting group title	Orteronel 400 mg + Prednisone 5 mg

Reporting group description:

Orteronel 400 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study. In Japan, subjects were administered with Orteronel 300 mg, tablets, orally, BID and Prednisone 5 mg, tablets, orally, BID for up to Day 28 of each treatment cycle throughout the study.

Serious adverse events	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	321 / 770 (41.69%)	380 / 784 (48.47%)	
number of deaths (all causes)	76	75	
number of deaths resulting from adverse events	9	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	25 / 770 (3.25%)	24 / 784 (3.06%)	
occurrences causally related to treatment / all	0 / 27	0 / 28	
deaths causally related to treatment / all	0 / 19	0 / 19	
Prostate cancer metastatic			
subjects affected / exposed	1 / 770 (0.13%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	
Metastatic pain			

subjects affected / exposed	7 / 770 (0.91%)	12 / 784 (1.53%)	
occurrences causally related to treatment / all	0 / 9	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	4 / 770 (0.52%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to biliary tract			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bladder			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to small intestine			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to rectum			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to urinary tract			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			

subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	3 / 770 (0.39%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (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	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder adenocarcinoma			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Throat cancer			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromatosis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 770 (0.65%)	9 / 784 (1.15%)	
occurrences causally related to treatment / all	2 / 6	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 770 (0.13%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 770 (0.00%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Shock			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flushing			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			

subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphoedema			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 770 (0.26%)	11 / 784 (1.40%)	
occurrences causally related to treatment / all	0 / 2	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 770 (0.13%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 770 (0.78%)	9 / 784 (1.15%)	
occurrences causally related to treatment / all	0 / 8	1 / 11	
deaths causally related to treatment / all	0 / 2	0 / 1	
Multi-organ failure			
subjects affected / exposed	3 / 770 (0.39%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	2 / 4	2 / 5	
deaths causally related to treatment / all	1 / 2	1 / 2	
Multi-organ disorder			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 770 (0.39%)	6 / 784 (0.77%)	
occurrences causally related to treatment / all	1 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 770 (0.13%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discomfort			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abasia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (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	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal oedema			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	23 / 770 (2.99%)	27 / 784 (3.44%)	
occurrences causally related to treatment / all	11 / 24	11 / 27	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea			
subjects affected / exposed	5 / 770 (0.65%)	7 / 784 (0.89%)	
occurrences causally related to treatment / all	1 / 5	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea exertional			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atelectasis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 770 (0.39%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 770 (0.26%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pharyngeal pouch			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood disorder due to a general medical condition			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	5 / 770 (0.65%)	7 / 784 (0.89%)	
occurrences causally related to treatment / all	5 / 5	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzymes increased			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			

subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 770 (0.00%)	6 / 784 (0.77%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood calcium increased			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (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			

Femoral neck fracture			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
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	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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	0 / 770 (0.00%)	1 / 784 (0.13%)	
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	3 / 770 (0.39%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural haematoma			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	6 / 770 (0.78%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal injury			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 770 (0.13%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured ischium			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pulmonary embolism			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stricture postoperative			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 770 (0.39%)	7 / 784 (0.89%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	5 / 770 (0.65%)	5 / 784 (0.64%)	
occurrences causally related to treatment / all	1 / 5	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Angina pectoris			
subjects affected / exposed	4 / 770 (0.52%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Stress cardiomyopathy			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	18 / 770 (2.34%)	14 / 784 (1.79%)	
occurrences causally related to treatment / all	6 / 20	3 / 15	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 770 (0.39%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 770 (0.00%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	7 / 770 (0.91%)	8 / 784 (1.02%)	
occurrences causally related to treatment / all	1 / 7	2 / 8	
deaths causally related to treatment / all	0 / 3	0 / 4	
Cardiac failure acute			
subjects affected / exposed	3 / 770 (0.39%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			

subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiopulmonary failure			
subjects affected / exposed	3 / 770 (0.39%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Arrhythmia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 770 (0.39%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coronary artery disease			

subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomegaly			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypertrophy			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiotoxicity			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conduction disorder			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	8 / 770 (1.04%)	5 / 784 (0.64%)	
occurrences causally related to treatment / all	3 / 12	0 / 6	
deaths causally related to treatment / all	1 / 5	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic stroke			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Syncope			
subjects affected / exposed	5 / 770 (0.65%)	7 / 784 (0.89%)	
occurrences causally related to treatment / all	1 / 5	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	11 / 770 (1.43%)	6 / 784 (0.77%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular pain			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 770 (0.00%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nystagmus			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve disorder			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tremor			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (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	18 / 770 (2.34%)	18 / 784 (2.30%)	
occurrences causally related to treatment / all	0 / 25	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 1	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphadenopathy			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 770 (0.52%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 770 (0.78%)	9 / 784 (1.15%)	
occurrences causally related to treatment / all	0 / 6	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 770 (0.39%)	9 / 784 (1.15%)	
occurrences causally related to treatment / all	0 / 3	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 770 (0.65%)	12 / 784 (1.53%)	
occurrences causally related to treatment / all	1 / 5	11 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 770 (0.26%)	8 / 784 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 770 (0.00%)	5 / 784 (0.64%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 770 (0.00%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	4 / 770 (0.52%)	7 / 784 (0.89%)	
occurrences causally related to treatment / all	0 / 5	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 770 (0.00%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 770 (0.39%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallstone ileus			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	3 / 770 (0.39%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastric haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 770 (0.52%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal stenosis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			

subjects affected / exposed	0 / 770 (0.00%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	6 / 770 (0.78%)	9 / 784 (1.15%)	
occurrences causally related to treatment / all	1 / 7	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 770 (0.39%)	7 / 784 (0.89%)	
occurrences causally related to treatment / all	0 / 3	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 770 (0.00%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	20 / 770 (2.60%)	13 / 784 (1.66%)	
occurrences causally related to treatment / all	1 / 22	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary hesitation			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pollakiuria			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	16 / 770 (2.08%)	8 / 784 (1.02%)	
occurrences causally related to treatment / all	2 / 21	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	6 / 770 (0.78%)	5 / 784 (0.64%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	3 / 770 (0.39%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydroureter			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			

subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder outlet obstruction			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder rupture			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis noninfective			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery thrombosis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 770 (0.00%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyrotoxic crisis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 770 (1.04%)	12 / 784 (1.53%)	
occurrences causally related to treatment / all	0 / 8	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	3 / 770 (0.39%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Flank pain			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	4 / 770 (0.52%)	6 / 784 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	2 / 770 (0.26%)	5 / 784 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	8 / 770 (1.04%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	1 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	2 / 770 (0.26%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	4 / 770 (0.52%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint destruction			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (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	1 / 770 (0.13%)	0 / 784 (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			
Pneumonia			
subjects affected / exposed	9 / 770 (1.17%)	30 / 784 (3.83%)	
occurrences causally related to treatment / all	2 / 9	5 / 35	
deaths causally related to treatment / all	0 / 0	1 / 4	
Lobar pneumonia			
subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 770 (0.13%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Bronchitis			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	3 / 770 (0.39%)	12 / 784 (1.53%)	
occurrences causally related to treatment / all	0 / 3	5 / 17	
deaths causally related to treatment / all	0 / 2	2 / 6	
Urosepsis			
subjects affected / exposed	4 / 770 (0.52%)	6 / 784 (0.77%)	
occurrences causally related to treatment / all	1 / 4	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 770 (0.26%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 2	
Bacteraemia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	9 / 770 (1.17%)	13 / 784 (1.66%)	
occurrences causally related to treatment / all	2 / 11	2 / 21	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	4 / 770 (0.52%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 770 (0.26%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis gangrenous			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abscess limb			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (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 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 770 (0.26%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 770 (0.13%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 770 (0.26%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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 / 770 (0.00%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle abscess			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
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	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Borrelia infection			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue abscess			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	8 / 770 (1.04%)	11 / 784 (1.40%)	
occurrences causally related to treatment / all	1 / 8	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypovolaemia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 770 (0.26%)	8 / 784 (1.02%)	
occurrences causally related to treatment / all	2 / 2	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			

subjects affected / exposed	0 / 770 (0.00%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 770 (0.00%)	5 / 784 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 770 (0.13%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 770 (0.00%)	6 / 784 (0.77%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 770 (0.00%)	4 / 784 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 770 (0.00%)	3 / 784 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	5 / 770 (0.65%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	5 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 770 (0.39%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

subjects affected / exposed	0 / 770 (0.00%)	2 / 784 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	2 / 770 (0.26%)	1 / 784 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Failure to thrive			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 770 (0.26%)	0 / 784 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Prednisone 5 mg	Orteronel 400 mg + Prednisone 5 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	721 / 770 (93.64%)	757 / 784 (96.56%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	80 / 770 (10.39%)	98 / 784 (12.50%)	
occurrences (all)	92	110	
Hot flush			
subjects affected / exposed	77 / 770 (10.00%)	81 / 784 (10.33%)	
occurrences (all)	85	87	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	173 / 770 (22.47%)	269 / 784 (34.31%)	
occurrences (all)	207	360	
Asthenia			

subjects affected / exposed	70 / 770 (9.09%)	106 / 784 (13.52%)	
occurrences (all)	93	138	
Oedema peripheral			
subjects affected / exposed	85 / 770 (11.04%)	86 / 784 (10.97%)	
occurrences (all)	97	109	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	41 / 770 (5.32%)	84 / 784 (10.71%)	
occurrences (all)	49	106	
Cough			
subjects affected / exposed	58 / 770 (7.53%)	62 / 784 (7.91%)	
occurrences (all)	66	71	
Dyspnoea exertional			
subjects affected / exposed	22 / 770 (2.86%)	41 / 784 (5.23%)	
occurrences (all)	24	46	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	65 / 770 (8.44%)	84 / 784 (10.71%)	
occurrences (all)	70	90	
Depression			
subjects affected / exposed	23 / 770 (2.99%)	56 / 784 (7.14%)	
occurrences (all)	23	57	
Investigations			
Lipase increased			
subjects affected / exposed	35 / 770 (4.55%)	179 / 784 (22.83%)	
occurrences (all)	53	243	
Weight decreased			
subjects affected / exposed	54 / 770 (7.01%)	124 / 784 (15.82%)	
occurrences (all)	64	153	
Amylase increased			
subjects affected / exposed	27 / 770 (3.51%)	146 / 784 (18.62%)	
occurrences (all)	41	199	
Blood creatinine increased			
subjects affected / exposed	21 / 770 (2.73%)	78 / 784 (9.95%)	
occurrences (all)	25	97	
Alanine aminotransferase increased			

subjects affected / exposed	14 / 770 (1.82%)	49 / 784 (6.25%)	
occurrences (all)	14	63	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	47 / 770 (6.10%)	57 / 784 (7.27%)	
occurrences (all)	57	70	
Nervous system disorders			
Dizziness			
subjects affected / exposed	50 / 770 (6.49%)	105 / 784 (13.39%)	
occurrences (all)	57	140	
Headache			
subjects affected / exposed	50 / 770 (6.49%)	70 / 784 (8.93%)	
occurrences (all)	71	83	
Dysgeusia			
subjects affected / exposed	15 / 770 (1.95%)	46 / 784 (5.87%)	
occurrences (all)	16	49	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	90 / 770 (11.69%)	75 / 784 (9.57%)	
occurrences (all)	113	92	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	130 / 770 (16.88%)	281 / 784 (35.84%)	
occurrences (all)	162	439	
Constipation			
subjects affected / exposed	129 / 770 (16.75%)	261 / 784 (33.29%)	
occurrences (all)	159	332	
Diarrhoea			
subjects affected / exposed	110 / 770 (14.29%)	221 / 784 (28.19%)	
occurrences (all)	149	341	
Vomiting			
subjects affected / exposed	115 / 770 (14.94%)	174 / 784 (22.19%)	
occurrences (all)	166	317	
Abdominal pain			
subjects affected / exposed	40 / 770 (5.19%)	72 / 784 (9.18%)	
occurrences (all)	48	82	

Dyspepsia			
subjects affected / exposed	33 / 770 (4.29%)	60 / 784 (7.65%)	
occurrences (all)	36	65	
Abdominal pain upper			
subjects affected / exposed	39 / 770 (5.06%)	51 / 784 (6.51%)	
occurrences (all)	48	65	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	45 / 770 (5.84%)	43 / 784 (5.48%)	
occurrences (all)	55	57	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	196 / 770 (25.45%)	158 / 784 (20.15%)	
occurrences (all)	260	207	
Muscle spasms			
subjects affected / exposed	118 / 770 (15.32%)	171 / 784 (21.81%)	
occurrences (all)	171	269	
Arthralgia			
subjects affected / exposed	122 / 770 (15.84%)	123 / 784 (15.69%)	
occurrences (all)	155	207	
Pain in extremity			
subjects affected / exposed	93 / 770 (12.08%)	79 / 784 (10.08%)	
occurrences (all)	111	99	
Bone pain			
subjects affected / exposed	75 / 770 (9.74%)	65 / 784 (8.29%)	
occurrences (all)	92	82	
Musculoskeletal pain			
subjects affected / exposed	64 / 770 (8.31%)	55 / 784 (7.02%)	
occurrences (all)	74	66	
Musculoskeletal chest pain			
subjects affected / exposed	42 / 770 (5.45%)	51 / 784 (6.51%)	
occurrences (all)	51	59	
Muscular weakness			
subjects affected / exposed	42 / 770 (5.45%)	42 / 784 (5.36%)	
occurrences (all)	49	47	
Myalgia			

subjects affected / exposed	39 / 770 (5.06%)	45 / 784 (5.74%)	
occurrences (all)	43	59	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	60 / 770 (7.79%)	58 / 784 (7.40%)	
occurrences (all)	90	73	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	86 / 770 (11.17%)	170 / 784 (21.68%)	
occurrences (all)	98	206	
Diabetes mellitus			
subjects affected / exposed	23 / 770 (2.99%)	45 / 784 (5.74%)	
occurrences (all)	30	50	
Hyperkalaemia			
subjects affected / exposed	15 / 770 (1.95%)	47 / 784 (5.99%)	
occurrences (all)	20	63	
Dehydration			
subjects affected / exposed	18 / 770 (2.34%)	42 / 784 (5.36%)	
occurrences (all)	24	53	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported