Clinical trial results:
A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or Following Docetaxel-Based Therapy

Summary

EudraCT number	2010-018662-23
Trial protocol	FR EE BE SK SE FI LT NL CZ ES AT GB PT IE GR DE IT BG
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	16 March 2017
First version publication date	16 March 2017

Trial information

Trial identification

Sponsor protocol code	C21005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01193257
WHO universal trial number (UTN)	U1111-1181-8040

Notes:

Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc.
Sponsor organisation address	40 Landsdowne Street, Cambridge, MA, United States, 02139
Public contact	Study Manager, Millennium Pharmaceuticals, Inc., 001 866-835-2233, GlobalOncologyMedinfo@takeda.com
Scientific contact	Study Manager, Millennium Pharmaceuticals, Inc., 001 866-835-2233, GlobalOncologyMedinfo@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	16 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if orteronel plus prednisone improved overall survival.

Protection of trial subjects:

Yes

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	United States: 80
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belarus: 10
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 79
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Greece: 60
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Lithuania: 31
Country: Number of subjects enrolled	Netherlands: 18

Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Sweden: 26
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	United Kingdom: 107
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Australia: 94
Country: Number of subjects enrolled	Brazil: 119
Country: Number of subjects enrolled	Chile: 12
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Japan: 50
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	South Africa: 18
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Korea, Republic of: 33
Worldwide total number of subjects	1099
EEA total number of subjects	569

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)	303
From 65 to 84 years	780
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 260 investigative sites in North America, Europe, Argentina, Australia, Brazil, Chile, China, Colombia, Israel, Japan, Mexico, New Zealand, Singapore, South Africa, South Korea, and Taiwan from 15 November 2010 to 29 February 2016.

Pre-assignment

Screening details:

Male subjects with a historical diagnosis of metastatic-castration resistant prostate cancer (mCRPC) that has progressed during or following docetaxel-based therapy were enrolled in 1 of 2 treatment groups: Orteronel 400 mg + Prednisone 5 mg or Placebo + Prednisone 5 mg.

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	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Prednisone

Arm description:

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

Arm type	Placebo
Investigational medicinal product name	Orteronel (TAK-700)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Orteronel placebo-matching tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

Arm title	Orteronel + Prednisone

Arm description:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

Arm type	Experimental
Investigational medicinal product name	Orteronel (TAK-700)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

Number of subjects in period 1	Placebo + Prednisone	Orteronel + Prednisone
Started	365	734
Treated	363	732
Completed	0	0
Not completed	365	734
Adverse event, serious fatal	202	391
Consent withdrawn by subject	26	86
Unblinded due to futility	135	251
Study termination by sponsor	-	3
Lost to follow-up	2	3

Baseline characteristics

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

Reporting group values	Placebo + Prednisone	Orteronel + Prednisone	Total
Number of subjects	365	734	1099
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)	103	200	303
From 65-84 years	256	524	780
85 years and over	6	10	16
Age Continuous Units: years			
arithmetic mean	69.4	69.2	
standard deviation	± 7.95	± 7.82	-
Gender, Male/Female Units: participants			
Female	0	0	0
Male	365	734	1099
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	4	5
Asian	48	77	125
Black or African American	9	18	27
White	305	620	925
Unknown or Not Reported	1	3	4
Other	1	12	13
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	45	107	152
Not Hispanic or Latino	302	588	890
Unknown or Not Reported	18	39	57

Region of Enrollment Units: Subjects			
Canada	11	21	32
United States	26	54	80
Austria	5	14	19
Belarus	6	4	10
Belgium	1	12	13
Bulgaria	1	3	4
Estonia	3	2	5
Finland	4	7	11
France	35	44	79
Germany	11	35	46
Greece	22	38	60
Hungary	2	7	9
Ireland	3	6	9
Italy	7	14	21
Portugal	8	8	16
Romania	0	12	12
Croatia	0	3	3
Czech Republic	1	1	2
Lithuania	9	22	31
Netherlands	6	12	18
Poland	5	17	22
Russia	2	2	4
Serbia	1	3	4
Slovakia	5	10	15
Spain	16	25	41
Sweden	10	16	26
Switzerland	1	2	3
United Kingdom	32	75	107
Argentina	1	8	9
Australia	28	66	94
Brazil	37	82	119
Chile	5	7	12
China	5	6	11
Colombia	0	4	4
Israel	5	9	14
Japan	17	33	50
Mexico	1	4	5
New Zealand	6	6	12
Singapore	1	1	2
South Africa	4	14	18
Taiwan, Province Of China	7	7	14
Korea, Republic Of	15	18	33
Study Specific Characteristic | Height			
Height data was available for 1096 participants as follows: n= 364, 732.			
Units: centimeter (cm)			
arithmetic mean	171.33	172.52	
standard deviation	± 7.675	± 7.156	-
Study Specific Characteristic | Weight			
Weight data was available for 1098 participants as follows: n= 365, 733.			
Units: kilogram (kg)			

arithmetic mean	79.85	82.77	
standard deviation	± 15.183	± 15.2	-
Study Specific Characteristic | Body mass index (BMI)			
BMI data was available for 1095 participants as follows: n= 364, 731.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	27.14	27.73	
standard deviation	± 4.491	± 4.37	-

End points

End points reporting groups

Reporting group title	Placebo + Prednisone

Reporting group description:

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

Reporting group title	Orteronel + Prednisone

Reporting group description:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

Primary: Overall Survival

End point title	Overall Survival

End point description:

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

End point type	Primary

End point timeframe:

Baseline until death (approximately up to 4.5 years)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: months				
median (confidence interval 95%)	15.3 (13.48 to 16.86)	17.1 (15.45 to 18.67)		

Statistical analyses

Statistical analysis title	Placebo and Orteronel

Statistical analysis description:

Hazard ratio is based on a stratified Cox’s proportional hazard regression model with stratification factors region (North America, Europe and Rest of World) and brief pain inventory-short form (BPI-SF) worst pain score at screening ([less than or equal to] <=4, greater than [>] 4) with treatment as a factor in the model. A hazard ratio less than 1 for the treatment indicates better prevention of the death in the Orteronel arm as compared to placebo arm.

Comparison groups	Placebo + Prednisone v Orteronel + Prednisone

Number of subjects included in analysis	1099
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.12085
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.875
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.739
upper limit	1.036

Secondary: Radiographic Progression-free Survival (rPFS)

End point title	Radiographic Progression-free Survival (rPFS)

End point description:

rPFS was defined as the time from randomization until radiographic disease progression or death due to any cause, whichever occurred first. Radiographic disease progression was defined as the occurrence of 1 or more of the following: The appearance of 2 or more new lesions on radionuclide bone scan as defined by prostate cancer working group (PCWG)2; Should 2 or more new bone lesions be evident at the first assessment (8-week assessment) on treatment, 2 or more additional new lesions must have been evident on a confirmatory assessment at least 6 weeks later; One or more new soft tissue/visceral organ lesions identified by computed tomography (CT)/magnetic resonance imaging (MRI); Progression as defined by response evaluation criteria in solid tumors (RECIST) 1.1 criteria. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: months				
median (confidence interval 95%)	5.7 (5.46 to 6.97)	8.3 (7.76 to 8.48)		

Statistical analyses

Statistical analysis title	Placebo and Orteronel

Statistical analysis description:

Hazard ratio is based on a stratified Cox’s proportional hazard regression model with stratification factors region (North America, Europe and Rest of World) and BPI-SF worst pain score at screening (<=4, >4) with treatment as a factor in the model. A hazard ratio less than 1 for the treatment indicates better prevention of the death in the Orteronel arm as compared to placebo arm.

Comparison groups	Placebo + Prednisone v Orteronel + Prednisone

Number of subjects included in analysis	1099
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.00038
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.653
upper limit	0.885

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 was defined as the percentage of subjects who had a PSA decline of at least 50 percent (%) from baseline. ITT population included all subejcts who were randomized.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: percentage of subjects				
number (not applicable)	9.9	24.9		

Statistical analyses

Statistical analysis title	Placebo and Orteronel

Statistical analysis description:

P-values test for odds ratio equal to 1.

Comparison groups	Placebo + Prednisone v Orteronel + Prednisone
Number of subjects included in analysis	1099
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0001
Method	Regression, Logistic

Secondary: Percentage of Subjects With Pain Response at Week 12

End point title	Percentage of Subjects With Pain Response at Week 12

End point description:

The pain response rate was calculated as the number of subjects with response divided by the number of ITT subjects in each treatment group (including those with missing data) times 100. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: percentage of subjects				
number (not applicable)	9	12.1		

Statistical analyses

Statistical analysis title	Placebo and Orteronel

Statistical analysis description:

P-values test for odds ratio equal to 1.

Comparison groups	Placebo + Prednisone v Orteronel + Prednisone
Number of subjects included in analysis	1099
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.12778
Method	Regression, Logistic

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

End point title	Number of Subjects Reporting one or More Treatment-emergent Adverse Events (TEAEs)

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 59 Day 58)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	732		
Units: subjects	345	719		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Physical Examination Findings

End point title	Number of Subjects With Abnormal Physical Examination Findings

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 59 Day 58)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	732		
Units: subjects	0	1		

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

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 59 Day 58)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	732		
Units: subjects				
Hypertension	21	83		
Hypotension	8	31		
Pyrexia	18	51		

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

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 59 Day 58)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	732		
Units: subjects				
Weight decreased	32	107		
Weight increased	7	6		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

ECOG assessed participant'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 ([greater than]>50% of waking 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% of waking hrs; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead. 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 End-of-treatment (EOT) (Cycle 59 Day 58)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	705		
Units: subjects				
Baseline: 0; Overall: 0	56	112		
Baseline: 0; Overall: 1	70	121		
Baseline: 0; Overall: 2	13	47		
Baseline: 0; Overall: 3	5	18		
Baseline: 0; Overall: 4	1	3		
Baseline: 1; Overall: 0	3	10		
Baseline: 1; Overall: 1	103	179		
Baseline: 1; Overall: 2	53	113		
Baseline: 1; Overall: 3	22	39		
Baseline: 1; Overall: 4	7	11		
Baseline: 2; Overall: 1	0	6		
Baseline: 2; Overall: 2	10	25		
Baseline: 2; Overall: 3	10	18		
Baseline: 2; Overall: 4	0	3		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG)

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:

Cycle 59 Day 58

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	732		
Units: subjects	1	3		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With TEAEs Categorized Into Investigations Related to Chemistry, Hematology or Steroid Hormone Panel
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 59 Day 58)	

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	732		
Units: subjects				
number (not applicable)				
Digestive enzymes	9	140		
Renal function analyses	13	41		
Liver function analyses	14	38		
Tissue enzyme analyses NEC	16	30		
Coagulation and bleeding analyses	1	17		
Mineral and electrolyte analyses	5	9		
White blood cell analyses	4	8		
Carbohydrate tolerance analyses(includingdiabetes)	0	8		
Urinary tract function analyses NEC	1	5		
Platelet analyses	3	4		
Cholesterol analyses	1	4		
Red blood cell analyses	2	3		
Protein analyses not else where classified (NEC)	0	3		
Vascular tests NEC (including blood pressure)	3	2		
Adrenal cortex tests	0	2		
Metabolism tests NEC	0	2		
Skeletal and cardiac muscle analyses	0	2		
Triglyceride analyses	0	1		
Urinalysis NEC	0	1		
Vitamin analyses	0	1		

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 was defined as the percentage of subjects who had a PSA decline of at least 50% 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, and 25

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: subjects				
number (not applicable)				
Cycle 4 (n= 283; 559)	12.72	32.74		
Cycle 7 (n= 163; 403)	18.4	38.21		
Cycle 10 (n= 102; 267)	22.55	36.7		
Cycle 13 (n= 55; 171)	23.64	40.94		
Cycle 16 (n= 34; 107)	23.53	44.86		
Cycle 19 (n= 24; 68)	20.83	42.65		
Cycle 22 (n= 14; 36)	28.57	52.78		
Cycle 25 (n= 8; 16)	25	62.5		

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 was defined as the percentage of subjects who had a PSA decline of at least 90% from

baseline. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	559		
Units: percentage of subjects				
number (not applicable)	2.83	9.66		

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 was defined as the percentage of subjects who had a PSA decline of at least 90% from baseline. ITT population where baseline and post-baseline assessments were available. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Cycle: 7, 10, 13, 16, 19, 22, and 25

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: percentage of subjects				
number (not applicable)				
Cycle 7 (n=163; 403)	4.91	14.89		
Cycle 10 (n=102; 267)	6.86	14.23		
Cycle 13 (n=55; 171)	7.27	15.2		
Cycle 16 (n=34; 107)	5.88	19.63		
Cycle 19 (n=24; 68)	4.17	23.53		
Cycle 22 (n=14; 36)	0	27.78		
Cycle 25 (n=8; 16)	0	43.75		

Statistical analyses

No statistical analyses for this end point

Secondary: Best PSA Response at any Time During the Study

End point title	Best PSA Response at any Time During the Study

End point description:

The PSA50 was defined as the percentage of subjects who had a PSA decline of at least 50% from baseline. PSA90 was defined as the percentage of subjects who had a PSA decline of at least 90% from baseline.

End point type	Secondary

End point timeframe:

Cycle: 4, 7, 10, 13, 16, 19, 22, and 25

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[1] - Best PSA response was not evaluated due to change in planned analysis.

[2] - Best PSA response was not evaluated due to change in planned analysis.

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 25% and 2 nanogram per milliliter (ng/mL) or greater increase in PSA above the baseline assessment (if no PSA decline from the baseline assessment). ITT population included all subjects who were randomized.

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 4.5 years)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: months				
median (confidence interval 95%)	2.9 (2.83 to 2.9)	5.5 (4.4 to 5.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shifts From Baseline Between Favorable and Unfavorable Categories in Circulating Tumor Cell Count (CTC)

End point title	Number of Subjects With Shifts From Baseline Between Favorable and Unfavorable Categories in Circulating Tumor Cell Count (CTC)

End point description:

A favorable CTC count was defined as less than (<) 5 counts per (/) 7.5 mililiter (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 where baseline and post-baseline assessments were available. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline and EOT (Cycle 59 Day 58)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: subjects				
Baseline: Favorable; EOT: Favorable	27	63		
Baseline: Favorable; EOT: Unfavorable	30	40		
Baseline: Unfavorable; EOT: Favorable	8	23		
Baseline: Unfavorable; EOT: Unfavorable	92	141		

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. The overall objective response was defined as a CR or PR. 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(s) or short axis of lymph nodes. Response per RECIST-evaluable population was defined as a subset of subjects who had measurable disease by RECIST 1.1 at baseline.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	280		
Units: percentage of subjects				
number (not applicable)	2.7	17.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

Time to pain progression was defined as the time from subject randomization to the first assessment date of pain progression. Pain progression was defined as the occurrence of 1 of the following and 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 was >= 4 with a >= 2 point increase over baseline in BPI-SF worst pain score with stable or increased analgesic use; The BPI-SF worst pain score was >= 4 but not less than baseline with new or increased (relative to baseline) Step II or Step III analgesic use; The BPI-SF worst pain score was <= 3 but not less than baseline with new or increased (relative to baseline) Step III analgesic use. ITT population included all subjects who were randomized. For Placebo + Prednisone arm, 99999 is mentioned for upper limit of CI because the upper limit of CI was not estimable for this arm.

End point type	Secondary

End point timeframe:

Baseline until EOT visit or until end of short term follow-up, whichever occurred later (approximately up to 4.5 years)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: months				
median (confidence interval 95%)	22 (20.48 to 99999)	24.2 (18.24 to 24.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Response

End point title	Time to Pain Response

End point description:

Time to pain response was defined as the time from randomization until first pain response. Pain response was defined as the occurrence of 1 of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later: A >= 2 point reduction from baseline in BPI-SF worst pain score without an increase in analgesic use, or a 25% or more reduction in analgesic use from baseline without an increase in worst pain score from baseline.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[3] - No data reported, median time to pain response was not estimable,not reached in any treatment group.
[4] - No data reported, median time to pain response was not estimable,not reached in any treatment group.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Best Pain Response

End point title	Number of Subjects with Best Pain Response

End point description:

Best pain response was evaluated in subjects who had a pain response across the entire study were summarized by treatment group. The pain response was defined as a >=2-point reduction from baseline in BPI-SF worst pain score without an increase in analgesic use, or a 25% or more reduction in analgesic use from baseline without an increase in worst pain score from baseline. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death, whichever occurred first (approximately up to 4.5 years)

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: subjects	72	166		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Health-related Quality of Life (HRQOL) Response at Week 12

End point title	Percentage of Subjects with Health-related Quality of Life (HRQOL) Response at Week 12

End point description:

The Global health status or quality of life(QOL) was measured as HRQOL response rate at 12 weeks using 2-item global health status index of european organization for research and treatment of cancer-quality of life questionnaire-C30 (EORTC QLQ-C30) instrument. HRQOL response was defined as 17-point increase from baseline assessment on QOL index, after score had been linearly transformed to 0 to 100 scale. EORTC QLQ-C30: included 5 functional scales(physical, role, cognitive, emotional, and social),1 global health status,3 symptom scales (fatigue, pain, nausea/vomiting) and 6 single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea and financial difficulties). Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores averaged, transformed to 0-100 scale; higher score showed better level of functioning or greater degree of symptoms. ITT population included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + Prednisone	Orteronel + Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	734		
Units: percentage of subjects				
number (not applicable)	9.9	8.7		

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 double-blind study drug and no more than 30 days after the last dose of study drug.

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	Orteronel + Prednisone

Reporting group description:

Orteronel 400 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study. Only subjects in Japan were administered with orteronel 300 mg, tablets, orally, BID and prednisone 5 mg, tablets, orally, BID up to Day 28 of each treatment cycle throughout the study.

Reporting group title	Placebo + Prednisone

Reporting group description:

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

Serious adverse events	Orteronel + Prednisone	Placebo + Prednisone	
Total subjects affected by serious adverse events			
subjects affected / exposed	384 / 732 (52.46%)	148 / 363 (40.77%)	
number of deaths (all causes)	85	48	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	33 / 732 (4.51%)	24 / 363 (6.61%)	
occurrences causally related to treatment / all	0 / 42	0 / 29	
deaths causally related to treatment / all	0 / 20	0 / 20	
Prostate cancer metastatic			
subjects affected / exposed	6 / 732 (0.82%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 5	0 / 4	
Metastatic pain			

subjects affected / exposed	9 / 732 (1.23%)	5 / 363 (1.38%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	5 / 732 (0.68%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pulmonary embolism			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to the mediastinum			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow tumour cell infiltration			
subjects affected / exposed	1 / 732 (0.14%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer recurrent			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic renal cell carcinoma			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 732 (0.41%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Embolism			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	19 / 732 (2.60%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	2 / 24	2 / 6	
deaths causally related to treatment / all	0 / 7	0 / 1	
Multi-organ failure			

subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Disease progression			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 1	
Performance status decreased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	10 / 732 (1.37%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	6 / 10	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	10 / 732 (1.37%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	5 / 13	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	4 / 732 (0.55%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 732 (1.09%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	2 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 732 (0.41%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (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	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sudden death			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombosis in device			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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	1 / 732 (0.14%)	0 / 363 (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	20 / 732 (2.73%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	7 / 21	2 / 4	
deaths causally related to treatment / all	0 / 3	0 / 1	
Dyspnoea			
subjects affected / exposed	8 / 732 (1.09%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory distress			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	7 / 732 (0.96%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 2	
Acute respiratory failure			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Alveolitis allergic			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	4 / 732 (0.55%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	12 / 732 (1.64%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	13 / 13	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	5 / 732 (0.68%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	5 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzymes increased			
subjects affected / exposed	4 / 732 (0.55%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			

subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood cortisol decreased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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			
Hip fracture			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Humerus fracture			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related circulatory overload			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney rupture			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
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	5 / 732 (0.68%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 732 (0.55%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	2 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	9 / 732 (1.23%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	3 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	5 / 732 (0.68%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	4 / 732 (0.55%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			

subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrioventricular block complete			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	17 / 732 (2.32%)	9 / 363 (2.48%)	
occurrences causally related to treatment / all	0 / 20	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
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	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	8 / 732 (1.09%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	1 / 11	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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	5 / 732 (0.68%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	4 / 732 (0.55%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	4 / 732 (0.55%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 732 (2.87%)	9 / 363 (2.48%)	
occurrences causally related to treatment / all	3 / 22	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Anaemia of chronic disease			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	18 / 732 (2.46%)	6 / 363 (1.65%)	
occurrences causally related to treatment / all	11 / 20	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	13 / 732 (1.78%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	9 / 14	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	10 / 732 (1.37%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	2 / 13	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 732 (0.00%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	6 / 732 (0.82%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 732 (0.68%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 732 (0.00%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis intestinal haemorrhagic			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	12 / 732 (1.64%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	1 / 15	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	11 / 732 (1.50%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	6 / 13	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Postrenal failure			

subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 732 (0.27%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic kidney disease			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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	14 / 732 (1.91%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	0 / 15	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urge incontinence			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Micturition urgency			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	9 / 732 (1.23%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	0 / 12	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	3 / 732 (0.41%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Azotaemia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urethral			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 732 (0.00%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			

subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric rupture			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mineralocorticoid deficiency			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 732 (1.37%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	1 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	1 / 732 (0.14%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	8 / 732 (1.09%)	14 / 363 (3.86%)	
occurrences causally related to treatment / all	0 / 10	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubic pain			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	7 / 732 (0.96%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	4 / 732 (0.55%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			

subjects affected / exposed	3 / 732 (0.41%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 732 (0.00%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	14 / 732 (1.91%)	3 / 363 (0.83%)	
occurrences causally related to treatment / all	1 / 17	1 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Urosepsis			

subjects affected / exposed	12 / 732 (1.64%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 13	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	7 / 732 (0.96%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	0 / 8	1 / 6	
deaths causally related to treatment / all	0 / 2	0 / 2	
Bacteraemia			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	19 / 732 (2.60%)	9 / 363 (2.48%)	
occurrences causally related to treatment / all	5 / 24	1 / 11	
deaths causally related to treatment / all	0 / 4	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	3 / 732 (0.41%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopneumonia			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lobar pneumonia			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	20 / 732 (2.73%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	0 / 25	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	4 / 732 (0.55%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	3 / 732 (0.41%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 732 (0.68%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
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	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess oral			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (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 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Listeriosis			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 732 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	15 / 732 (2.05%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	3 / 18	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	10 / 732 (1.37%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	5 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	10 / 732 (1.37%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	8 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	4 / 732 (0.55%)	4 / 363 (1.10%)	
occurrences causally related to treatment / all	2 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	3 / 732 (0.41%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	2 / 732 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	2 / 732 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 732 (0.14%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 732 (0.14%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Orteronel + Prednisone	Placebo + Prednisone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	703 / 732 (96.04%)	341 / 363 (93.94%)	
Investigations			
Weight decreased			
subjects affected / exposed	113 / 732 (15.44%)	34 / 363 (9.37%)	
occurrences (all)	140	41	
Lipase increased			

subjects affected / exposed	113 / 732 (15.44%)	5 / 363 (1.38%)	
occurrences (all)	149	5	
Amylase increased			
subjects affected / exposed	101 / 732 (13.80%)	5 / 363 (1.38%)	
occurrences (all)	133	5	
Blood creatinine increased			
subjects affected / exposed	38 / 732 (5.19%)	9 / 363 (2.48%)	
occurrences (all)	50	11	
Vascular disorders			
Hypertension			
subjects affected / exposed	84 / 732 (11.48%)	22 / 363 (6.06%)	
occurrences (all)	98	23	
Hot flush			
subjects affected / exposed	63 / 732 (8.61%)	20 / 363 (5.51%)	
occurrences (all)	64	20	
Nervous system disorders			
Headache			
subjects affected / exposed	76 / 732 (10.38%)	23 / 363 (6.34%)	
occurrences (all)	89	30	
Dizziness			
subjects affected / exposed	78 / 732 (10.66%)	15 / 363 (4.13%)	
occurrences (all)	101	16	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	103 / 732 (14.07%)	59 / 363 (16.25%)	
occurrences (all)	133	80	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	223 / 732 (30.46%)	84 / 363 (23.14%)	
occurrences (all)	284	95	
Asthenia			
subjects affected / exposed	102 / 732 (13.93%)	39 / 363 (10.74%)	
occurrences (all)	145	44	
Oedema peripheral			
subjects affected / exposed	77 / 732 (10.52%)	45 / 363 (12.40%)	
occurrences (all)	94	48	

Pyrexia			
subjects affected / exposed	48 / 732 (6.56%)	18 / 363 (4.96%)	
occurrences (all)	57	23	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	319 / 732 (43.58%)	94 / 363 (25.90%)	
occurrences (all)	456	115	
Vomiting			
subjects affected / exposed	272 / 732 (37.16%)	60 / 363 (16.53%)	
occurrences (all)	541	83	
Constipation			
subjects affected / exposed	222 / 732 (30.33%)	64 / 363 (17.63%)	
occurrences (all)	279	74	
Diarrhoea			
subjects affected / exposed	201 / 732 (27.46%)	54 / 363 (14.88%)	
occurrences (all)	286	65	
Abdominal pain			
subjects affected / exposed	46 / 732 (6.28%)	21 / 363 (5.79%)	
occurrences (all)	57	26	
Dyspepsia			
subjects affected / exposed	46 / 732 (6.28%)	13 / 363 (3.58%)	
occurrences (all)	56	14	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	67 / 732 (9.15%)	21 / 363 (5.79%)	
occurrences (all)	80	22	
Cough			
subjects affected / exposed	63 / 732 (8.61%)	19 / 363 (5.23%)	
occurrences (all)	69	22	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	67 / 732 (9.15%)	26 / 363 (7.16%)	
occurrences (all)	75	26	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	139 / 732 (18.99%)	62 / 363 (17.08%)	
occurrences (all)	196	85	
Arthralgia			
subjects affected / exposed	112 / 732 (15.30%)	55 / 363 (15.15%)	
occurrences (all)	150	71	
Bone pain			
subjects affected / exposed	89 / 732 (12.16%)	51 / 363 (14.05%)	
occurrences (all)	117	61	
Muscle spasms			
subjects affected / exposed	110 / 732 (15.03%)	27 / 363 (7.44%)	
occurrences (all)	167	31	
Pain in extremity			
subjects affected / exposed	86 / 732 (11.75%)	45 / 363 (12.40%)	
occurrences (all)	116	57	
Musculoskeletal pain			
subjects affected / exposed	57 / 732 (7.79%)	24 / 363 (6.61%)	
occurrences (all)	73	30	
Myalgia			
subjects affected / exposed	39 / 732 (5.33%)	20 / 363 (5.51%)	
occurrences (all)	46	22	
Muscular weakness			
subjects affected / exposed	36 / 732 (4.92%)	21 / 363 (5.79%)	
occurrences (all)	40	23	
Musculoskeletal chest pain			
subjects affected / exposed	39 / 732 (5.33%)	16 / 363 (4.41%)	
occurrences (all)	44	18	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	57 / 732 (7.79%)	24 / 363 (6.61%)	
occurrences (all)	75	29	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	208 / 732 (28.42%)	68 / 363 (18.73%)	
occurrences (all)	249	75	
Hypokalaemia			

subjects affected / exposed occurrences (all)	45 / 732 (6.15%) 52	14 / 363 (3.86%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2011	Revised minimum prior docetaxel exposure received within a 6-month period for subjects with progressive disease and that subjects must have received 1 or 2 lines or regimens of prior therapy; Eliminated washout period for discontinued prior antiandrogen therapy for subjects enrolling in study; Clarified that dose modifications applied to blinded study drug; and subjects with asymptomatic Grade 3/4 laboratory findings not related to study drug may not have required dose modification; Clarified that subjects must receive first dose of study drug within 7 days of randomization, documentation demonstrating that subject had progressive disease must have been submitted to the sponsor along with a Patient Eligibility Worksheet and information on medications being taken at time of screening was not collected; Added an early interim analysis to occur after approximately 50% of planned events; Clarified that evaluation of pain was to be performed at unscheduled visits; Updated the contact information for reporting of SAEs; Clarified the collection period for SAEs; Clarified the radiographic disease assessments according to the PCWG2 and modified RECIST; Updated safety information from ongoing clinical trials with Orteronel; Updated the PSA data from Study TAK-700_201; Provided the rationale for enumeration of CTCs; Clarified the rationale for genotyping and assessment of biomarkers in tumor tissue; Updated information on the potential risks of Orteronel.
22 June 2011	Clarified that dose modifications were required for Grade 3 or 4 AEs or intolerable Grade 2 AEs that were considered at least possibly related to study drug.
26 March 2013	Updated procedures for recording and reporting AEs and SAEs to be consistent with the sponsor's current procedures; Updated details on the monitoring of AEs throughout the study to be consistent with the sponsor's current procedures; Clarified that a listing of TEAEs resulting in study drug discontinuation would be provided; Updated status of ongoing clinical trials with orteronel to include Studies C21004, C21008, C21009, C21012, and C21013; Added background information on enzalutamide and abiraterone acetate to the study rationale; Updated the risk language of orteronel, per the most recent Investigator Brochure data cutoff date, 29 September 2012; Updated pancreas-related SAEs, per the most recent Investigator Brochure data cutoff date, 29 September 2012; Updated the risk language for T-1358043 (a process impurity, drug product degradant, and minor metabolite of orteronel) based on nonclinical studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported