



Clinical trial results:

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Tasquinimod in Men with Metastatic Castrate Resistant Prostate Cancer Summary

EudraCT number	2010-021870-12
Trial protocol	SE GB BE DE LV NL CZ ES LT IT SK GR EE BG
Global end of trial date	07 August 2015

Results information

Result version number	v1 (current)
This version publication date	20 August 2016
First version publication date	20 August 2016
Summary attachment (see zip file)	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Tasquinimod in Men with Metastatic Castrate Resistant Prostate Cancer (TASQ_10TASQ10_1530116_SYNOPSIS.pdf)

Trial information

Trial identification

Sponsor protocol code	10TASQ10
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01234311
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Active Biotech AB
Sponsor organisation address	Scheelevagen 22, Lund, Sweden, 22007
Public contact	Clinical Trials at Active Biotech, Active Biotech AB, 46 46192000, clinicaltrials@activebiotech.com
Scientific contact	Clinical Trials at Active Biotech, Active Biotech AB, 46 46192000, clinicaltrials@activebiotech.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	13 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2015
Global end of trial reached?	Yes
Global end of trial date	07 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to confirm the effect of tasquinimod on delaying disease progression or death compared with placebo.

Protection of trial subjects:

Regular review by IDMC of unblinded safety data

Background therapy:

Castrate level of testosterone

Evidence for comparator:

Placebo used as comparator in the pre-chemotherapy setting

Actual start date of recruitment	29 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Romania: 51
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	Spain: 68
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 71
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Latvia: 38
Country: Number of subjects enrolled	Lithuania: 31
Country: Number of subjects enrolled	United States: 198
Country: Number of subjects enrolled	Ukraine: 86
Country: Number of subjects enrolled	Turkey: 2

Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Panama: 12
Country: Number of subjects enrolled	New Zealand: 22
Country: Number of subjects enrolled	Mexico: 24
Country: Number of subjects enrolled	Lebanon: 6
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Israel: 42
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	China: 15
Country: Number of subjects enrolled	Chile: 18
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Brazil: 54
Country: Number of subjects enrolled	Australia: 51
Country: Number of subjects enrolled	Argentina: 8
Worldwide total number of subjects	1245
EEA total number of subjects	555

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)	266
From 65 to 84 years	911
85 years and over	68

Subject disposition

Recruitment

Recruitment details:

Recruitment was performed at 241 active sites in 37 countries across 4 regions, EMEA (Europe, Middle-East & Africa), NA (North America), LA (Latin America) and APAC (Asia Pacific) from 29 March 2011 until 7 December 2012.

Pre-assignment

Screening details:

Overall 1645 patients were screened and 1245 were randomly assigned, 2:1 to either tasquinimod or placebo.

Period 1

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

Blinding implementation details:

Tasquinimod and placebo was administered in a double-blind fashion. The PK analysis was conducted by an unblinded team, separate from the blinded study team. The results of PK analyses were not distributed to any member of the study team until after the blind was broken. The results of serum amylase, fibrinogen, CRP, lactate dehydrogenase, and serum lipase were not distributed by the central laboratory until after the blind was broken

Arms

Are arms mutually exclusive?	Yes
Arm title	Tasquinimod arm

Arm description:

Patients receiving tasquinimod treatment

Arm type	Experimental
Investigational medicinal product name	Tasquinimod
Investigational medicinal product code	ABR-215050
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Once daily dosing. Patients began at a dose of 0.25 mg/day of tasquinimod (or matching placebo for patients in Treatment Group B) for at least 2 weeks. Once tolerability of the 0.25 mg/day dose was established, patients received a dose increase to 0.5 mg/day for at least 2 weeks, and then increase to 1 mg/day of study drug. Patients showing poor tolerability for the escalated doses were allowed to continue study treatment at the highest individually tolerated dose. Treatment continued until any criterion for withdrawal from study treatment was fulfilled

Arm title	Placebo arm
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Arm description:

Patients receiving placebo

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

Dosage and administration details:

Matching placebo

Number of subjects in period 1	Tasquinimod arm	Placebo arm
Started	832	413
Completed	832	413

Baseline characteristics

Reporting groups

Reporting group title	Tasquinimod arm
Reporting group description:	
Patients receiving tasquinimod treatment	
Reporting group title	Placebo arm
Reporting group description:	
Patients receiving placebo	

Reporting group values	Tasquinimod arm	Placebo arm	Total
Number of subjects	832	413	1245
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	176	90	266
From 65-84 years	613	298	911
85 years and over	43	25	68
Age continuous			
Units: years			
median	71	71	
full range (min-max)	43 to 92	48 to 92	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	832	413	1245
Race			
Units: Subjects			
White	729	359	1088
Black	20	8	28
Asian	46	27	73
American indian or Alaska native	13	8	21
Native Hawaian or other Pacific islander	1	0	1
Other	23	10	33
Missing	0	1	1
Region			
Units: Subjects			
North America	143	72	215
Europe, Middle East and Africa (EMEA)	505	254	759
Asia Pacific (APAC)	94	46	140
Latin America	90	41	131

Karnofsky performance score Units: Subjects			
<90%	187	95	282
>/=90%	645	318	963
Visual Analogue Scale (VAS) score for tumour related pain Units: Subjects			
0-0	371	195	566
1-3	286	157	443
4-10	155	60	215
Missing	20	1	21
Time since diagnosis of prostate cancer Units: Months			
median	45.75	57.7	
full range (min-max)	0.1 to 299.6	0.3 to 319.9	-

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients	

Reporting group values	ITT		
Number of subjects	1245		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	266		
From 65-84 years	911		
85 years and over	68		
Age continuous Units: years			
median	71		
full range (min-max)	43 to 92		
Gender categorical Units: Subjects			
Female	0		
Male	1245		
Race Units: Subjects			
White	1088		
Black	28		
Asian	73		
American indian or Alaska native	21		

Native Hawaiian or other Pacific islander	1		
Other	33		
Missing	1		
Region			
Units: Subjects			
North America	215		
Europe, Middle East and Africa (EMEA)	759		
Asia Pacific (APAC)	140		
Latin America	131		
Karnofsky performance score			
Units: Subjects			
<90%	282		
>/=90%	963		
Visual Analogue Scale (VAS) score for tumour related pain			
Units: Subjects			
0-0	566		
1-3	443		
4-10	215		
Missing	21		
Time since diagnosis of prostate cancer			
Units: Months			
median	49.3		
full range (min-max)	0.1 to 319.9		

End points

End points reporting groups

Reporting group title	Tasquinimod arm
Reporting group description: Patients receiving tasquinimod treatment	
Reporting group title	Placebo arm
Reporting group description: Patients receiving placebo	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients	

Primary: Radiographic Progression Free Survival (rPFS)

End point title	Radiographic Progression Free Survival (rPFS)
End point description: Radiological progression is defined by any of the following criteria: • Progression of soft tissue lesions according to RECIST 1.1 • Progression of bone lesions detected with bone scan according to PCWG2 criteria • Radiologically confirmed spinal cord compression or pathological fracture due to malignant progression	
End point type	Primary
End point timeframe: rPFS is defined as the time from the date of randomization to the date of radiological progression or death	

End point values	Tasquinimod arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	832	413		
Units: Months				
median (confidence interval 95%)	7 (5.8 to 8.2)	4.4 (3.5 to 5.5)		

Statistical analyses

Statistical analysis title	rPFS, Primary endpoint
Comparison groups	Tasquinimod arm v Placebo arm
Number of subjects included in analysis	1245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

End point type	Secondary
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End point timeframe:

OS is defined as the time from the date of randomization to the date of death due to any cause

End point values	Tasquinimod arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	832	413		
Units: Months				
median (confidence interval 95%)	21.3 (19.5 to 23)	24 (21.4 to 26.9)		

Statistical analyses

Statistical analysis title	OS, Key secondary endpoint
Comparison groups	Tasquinimod arm v Placebo arm
Number of subjects included in analysis	1245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed from the time the patient signs the ICF until 30 days after the last dose of study drug or until starting a new antineoplastic agent.

Adverse event reporting additional description:

At every study visit, patients were asked a standard question to elicit any medically related changes in their well-being. They were also asked if they had been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens, including prescription, over-the-counter, and herbal medications and supplements.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Tasquinimod arm
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Reporting group description:

Patients receiving tasquinimod treatment

Reporting group title	Placebo arm
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Reporting group description:

Patients receiving placebo

Serious adverse events	Tasquinimod arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	229 / 830 (27.59%)	97 / 411 (23.60%)	
number of deaths (all causes)	492	238	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	3 / 830 (0.36%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage 0			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour invasion			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral neoplasm			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral neoplasm			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteritis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 830 (0.24%)	3 / 411 (0.73%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboangiitis obliterans			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 830 (0.72%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 830 (0.48%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Device breakage			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			

subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 830 (0.12%)	11 / 411 (2.68%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	5 / 830 (0.60%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granuloma			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	3 / 830 (0.36%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 830 (0.60%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	4 / 830 (0.48%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic obstruction			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 830 (0.48%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 830 (0.36%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 830 (0.60%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 830 (0.24%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory arrest			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 830 (0.12%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteoradionecrosis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scratch			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
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 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 830 (0.24%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 830 (0.12%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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	11 / 830 (1.33%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	9 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 830 (0.36%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 830 (0.48%)	13 / 411 (3.16%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	4 / 830 (0.48%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	3 / 830 (0.36%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrhythmia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	101 / 830 (12.17%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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 / 830 (0.12%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 830 (0.36%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 830 (0.12%)	3 / 411 (0.73%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	27 / 830 (3.25%)	12 / 411 (2.92%)	
occurrences causally related to treatment / all	4 / 35	1 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	3 / 830 (0.36%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochromic anaemia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 830 (0.24%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 830 (0.24%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	101 / 830 (12.17%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	6 / 830 (0.72%)	23 / 411 (5.60%)	
occurrences causally related to treatment / all	4 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 830 (0.12%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal stenosis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			

subjects affected / exposed	3 / 830 (0.36%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
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			

Angioedema			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neck obstruction			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder outlet obstruction			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis noninfective			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	4 / 830 (0.48%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	10 / 830 (1.20%)	8 / 411 (1.95%)	
occurrences causally related to treatment / all	1 / 11	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	10 / 830 (1.20%)	3 / 411 (0.73%)	
occurrences causally related to treatment / all	0 / 12	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower urinary tract symptoms			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocturia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pollakiuria			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 830 (0.36%)	3 / 411 (0.73%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	15 / 830 (1.81%)	3 / 411 (0.73%)	
occurrences causally related to treatment / all	3 / 16	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	16 / 830 (1.93%)	12 / 411 (2.92%)	
occurrences causally related to treatment / all	1 / 19	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	2 / 830 (0.24%)	4 / 411 (0.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract pain			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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			
Arthralgia			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	6 / 830 (0.72%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	101 / 830 (12.17%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle twitching			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 830 (0.24%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess oral			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	3 / 830 (0.36%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Candida pneumonia			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device related infection			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (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 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Erysipelas			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder empyema			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 830 (0.00%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 830 (1.20%)	4 / 411 (0.97%)	
occurrences causally related to treatment / all	0 / 10	2 / 4	
deaths causally related to treatment / all	0 / 1	1 / 2	
Pneumonia klebsiella			

subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis acute			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 830 (0.48%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	10 / 830 (1.20%)	2 / 411 (0.49%)	
occurrences causally related to treatment / all	0 / 11	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			

subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 830 (0.12%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 830 (0.60%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 830 (0.36%)	3 / 411 (0.73%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hyperammonaemia			
subjects affected / exposed	1 / 830 (0.12%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	3 / 830 (0.36%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 830 (0.00%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 830 (0.24%)	0 / 411 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 830 (0.00%)	3 / 411 (0.73%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 830 (0.36%)	1 / 411 (0.24%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	101 / 830 (12.17%)	0 / 411 (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	Tasquinimod arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	791 / 830 (95.30%)	381 / 411 (92.70%)	
Investigations			
Weight decreased			
subjects affected / exposed	125 / 830 (15.06%)	35 / 411 (8.52%)	
occurrences (all)	155	42	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain subjects affected / exposed occurrences (all)	263 / 830 (31.69%) 433	127 / 411 (30.90%) 233	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	65 / 830 (7.83%) 78	28 / 411 (6.81%) 35	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	168 / 830 (20.24%) 279	62 / 411 (15.09%) 96	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	137 / 830 (16.51%) 202 216 / 830 (26.02%) 306 85 / 830 (10.24%) 121 47 / 830 (5.66%) 55	51 / 411 (12.41%) 71 72 / 411 (17.52%) 87 28 / 411 (6.81%) 36 13 / 411 (3.16%) 19	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	50 / 830 (6.02%) 77 45 / 830 (5.42%) 54 191 / 830 (23.01%) 241	20 / 411 (4.87%) 24 17 / 411 (4.14%) 18 67 / 411 (16.30%) 76	

subjects affected / exposed	93 / 830 (11.20%)	41 / 411 (9.98%)	
occurrences (all)	116	52	
Dyspepsia			
subjects affected / exposed	45 / 830 (5.42%)	15 / 411 (3.65%)	
occurrences (all)	61	19	
Nausea			
subjects affected / exposed	222 / 830 (26.75%)	89 / 411 (21.65%)	
occurrences (all)	316	115	
Vomiting			
subjects affected / exposed	85 / 830 (10.24%)	27 / 411 (6.57%)	
occurrences (all)	109	36	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	70 / 830 (8.43%)	29 / 411 (7.06%)	
occurrences (all)	79	31	
Dyspnoea			
subjects affected / exposed	53 / 830 (6.39%)	15 / 411 (3.65%)	
occurrences (all)	59	19	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	87 / 830 (10.48%)	31 / 411 (7.54%)	
occurrences (all)	105	34	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	101 / 830 (12.17%)	52 / 411 (12.65%)	
occurrences (all)	143	68	
Back pain			
subjects affected / exposed	103 / 830 (12.41%)	38 / 411 (9.25%)	
occurrences (all)	124	46	
Muscular weakness			
subjects affected / exposed	44 / 830 (5.30%)	11 / 411 (2.68%)	
occurrences (all)	51	15	
Musculoskeletal pain			
subjects affected / exposed	59 / 830 (7.11%)	23 / 411 (5.60%)	
occurrences (all)	68	26	
Myalgia			

subjects affected / exposed occurrences (all)	62 / 830 (7.47%) 81	22 / 411 (5.35%) 24	
Pain in extremity subjects affected / exposed occurrences (all)	103 / 830 (12.41%) 144	31 / 411 (7.54%) 37	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	38 / 830 (4.58%) 46	13 / 411 (3.16%) 13	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	249 / 830 (30.00%) 313	66 / 411 (16.06%) 82	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2011	• To further clarify current treatment guidelines for castrate-resistant prostate cancer • To clarify the guidance given for supportive medication • To clarify that Follow-up Visits should only be performed for patients who have discontinued study drug treatment • To facilitate the collection of follow-up scans • To clarify the guidance given in the protocol (Exclusion Criteria 2 and Reasons for Withdrawal From Study Treatment) regarding use of potential new anticancer treatment • To reduce unnecessary exposure to radiation (from scans) of the heart region • To clarify criteria for evaluation of soft tissue lesions according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1) • To be consistent with published recommendation for evaluation of bone lesions according to Prostate Cancer Working Group 2 (PCWG2) criteria • To clarify the definition of pain criteria for symptomatic progression • To clarify that disease progression should not be reported as an adverse event (AE) • To improve guidance regarding implementation of the Common Terminology Criteria for Adverse Events (Version 4.0) (CTCAEv4.0) for AE grading • To clarify time points for collection of biobank samples in accordance with visit schedule • To clarify the recommendation to take the study drug with food • To clarify the set of quality-of-life tools to be used during Follow-up • To amend any typographical and formatting inconsistencies • To extend the guidance regarding collection of key secondary endpoint data • To further clarify withdrawal from study treatment based on symptomatic disease progression • To extend collection of radiological data for central review • To clarify the timing of procedures during the Screening Phase
20 March 2012	• To modify exclusion criterion to allow patients on warfarin with well controlled international normalized ratio (INR) to participate in the study • To clarify defined PSA progression criteria for inclusion in the study in accordance with the Prostate Cancer Working Group 2 (PCWG2) • To modify required washout period for Estracyt and Provenge in accordance with clinical relevance • To facilitate collection of baseline bone scan by allowing extended window • To clarify conditions for retesting of testosterone during screening • To introduce replacement of Global Project Manager • To introduce replacement of Medical Monitor • To introduce minor editorial changes

17 July 2013	• To update the regional contact details for adverse event reporting • To add additional secondary endpoints • To modify the planned analysis to allow the primary PFS analysis to be conducted at the same time as the first OS analyses (473 OS events), i.e. PFS will not be performed separately • To define OS as the key secondary endpoint • To introduce 2 event driven interim OS analyses (the first at 65% (473 events) and the second at 80% (582 events) of the final number of OS events (727) • To modify the allocation of alpha spending for the OS analyses to the O'Brien Fleming function as implemented by Lan DeMets • To recognize that the Data Safety Monitoring Board has been superseded by the Independent Data Monitoring Committee (IDMC) • To recognize that the commitment for a separate follow-up study protocol is removed, but at the final analysis the study drug will be made available to the patients who are benefiting from the treatment • To clarify and modify the censoring rules for the primary PFS from start of alternative antitumor therapy to the date of the previous scan assessment • To clarify that any analysis for specific regions will be described in the SAP • To amend any typographical and formatting inconsistencies • To introduce replacement of Global Project Manager • To clarify Per Protocol population definition
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: