Clinical trial results:
A Randomized Phase 3 Study Comparing Standard First-Line Docetaxel/Prednisone to Docetaxel/Prednisone in Combination with Custirsen (OGX-011) in Men with Metastatic Castrate Resistant Prostate Cancer

Summary

EudraCT number	2010-021011-16
Trial protocol	HU FR DE ES BE NL GB IT
Global end of trial date	30 June 2014

Results information

Result version number	v2 (current)
This version publication date	10 April 2016
First version publication date	07 August 2015
Version creation reason	• New data added to full data set • Correction of full data set add back-up user

Trial information

Trial identification

Sponsor protocol code	OGX-011-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01188187
WHO universal trial number (UTN)	-
Other trial identifiers	Teva: TV-1011/11

Notes:

Sponsors

Sponsor organisation name	OncoGenex Technologies Inc
Sponsor organisation address	1001 W Broadway, Suite 400, Vancouver, BC , Canada, V6H 4B1
Public contact	Director, Regulatory Affairs, OncoGenex Pharmaceuticals, Inc, 01 425-686-1500,
Scientific contact	Director, Regulatory Affairs, OncoGenex Pharmaceuticals, Inc, 01 425-686-1500,

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	24 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To ascertain whether the survival time distribution for patients randomized to the investigational arm is consistent with longer survival as compared to patients randomized to the control arm.

Protection of trial subjects:

The informed consent forms used for the study comply with the Declaration of Helsinki and its updates and the International Conference on Harmonization (ICH) Guidelines and have been approved by the Sponsor and the Investigator's IRB/EC/REB. The Investigator explained the nature of the study and the treatment in such a manner that the patient was aware of his/her rights and responsibilities, as well as potential benefits and risks. Patients were informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent was recorded in the patient's medical record or a study/clinic chart.
Patients, or their legally authorized representative, gave informed consent in writing prior to the performance of any protocol-specific procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2010
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: 21
Country: Number of subjects enrolled	Spain: 105
Country: Number of subjects enrolled	United Kingdom: 70
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	France: 133
Country: Number of subjects enrolled	Germany: 163
Country: Number of subjects enrolled	Hungary: 64
Country: Number of subjects enrolled	Italy: 58
Country: Number of subjects enrolled	Canada: 167
Country: Number of subjects enrolled	Israel: 35
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	United States: 148

Worldwide total number of subjects	1022
EEA total number of subjects	631

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)	305
From 65 to 84 years	705
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One thousand two hundred seventy patients were screened and 1022 randomized. Stratified randomization was used in order to minimize between-arm imbalance over two stratification factors: use of opioids for prostate cancer-related pain at screening (yes versus no) and radiographic evidence (e.g., CT or bone scan) of progression (yes versus no).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

A blinding plan for the Sponsor was implemented to minimize the chance of Sponsor decisions being affected by knowledge of the arm assignment of individual patients, knowledge of the results from the secondary outcome, or accumulating survival data. An unblinded independent Data Monitoring Committee, supported by an independent statistician monitored the progress of the study. Once the last patient completed treatment, the Sponsor was no longer blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Docetaxel/prednisone

Arm description:

Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day.
Treatment continued for 10 cycles or until unacceptable toxicity or disease progression.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel (75 mg/M^2) was administered IV on Day 1 of each 21 day cycle, for up to 10 treatment cycles or until unacceptable toxicity or disease progression.

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

Dosage and administration details:

Oral prednisone (5 mg twice daily for a total of 10 mg/day) began on Day 1 of Cycle 1 and continued, at a minimum, through the completion of the final treatment cycle.

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

Dosage and administration details:

Dexamethasone 8 mg by mouth twice a day for 3 days beginning one day before docetaxel

administration to reduce the incidence and severity of hypersensitivity reactions and fluid retention.

Arm title	Docetaxel/prednisone/custirsen

Arm description:

Three doses of 640 mg custirsen administered IV as a loading dose between Days -9 to -1. Custirsen, 640 mg, given IV weekly on Days 1, 8, and 15 of each 21 day cycle. Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day.
Treatment continued for 10 cycles or until unacceptable toxicity or disease progression .

Arm type	Experimental
Investigational medicinal product name	Custirsen
Investigational medicinal product code	
Other name	OGX-011
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Three doses of 640 mg custirsen were administered IV over 2 hours as loading doses during Days -9 to -1. There must have been at least one "non-infusion" day between each administration of custirsen (i.e. every other day) and between the third loading dose of custirsen and Day 1 of Cycle 1. There were no more than 7 days between the last loading dose and Day 1 of Cycle 1. A common schedule was to give the three loading doses of custirsen on Monday, Wednesday and Friday with Day 1, Cycle 1 starting on the following Monday.

During study dosing of custirsen consisted of weekly 640 mg intravenous injections on Days 1, 8, and 15 of each 21 day cycle for up to 10 treatment
cycles or until unacceptable toxicity or disease progression. Custirsen was administered prior to docetaxel on Day 1 of each cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel (75 mg/M^2) was administered IV on Day 1 of each 21 day cycle, for up to 10 treatment cycles or until unacceptable toxicity or disease progression.

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

Dosage and administration details:

Oral prednisone (5 mg twice daily for a total of 10 mg/day) began on Day 1 of Cycle 1 and continued, at a minimum, through the completion of the final treatment cycle.

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

Dosage and administration details:

Dexamethasone 8 mg by mouth twice a day for 3 days beginning one day before docetaxel administration to reduce the incidence and severity of hypersensitivity reactions and fluid retention.

Number of subjects in period 1	Docetaxel/prednisone	Docetaxel/prednisone/custirsen
Started	512	510
Completed	210	150
Not completed	302	360
Adverse event, serious fatal	3	1
Consent withdrawn by subject	35	42
Adverse event, non-fatal	146	210
Symptomatic deterioration	17	25
Progressive disease during loading dose	-	1
Not specified	8	5
Death - patient not treated	1	-
Not specified - patient not treated	6	4
Progressive disease	78	68
Lost to follow-up	1	-
Consent withdrawn by subject - patient not treated	6	4
Treatment delay > 3 weeks	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Docetaxel/prednisone
Reporting group description:	
Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day. Treatment continued for 10 cycles or until unacceptable toxicity or disease progression.	
Reporting group title	Docetaxel/prednisone/custirsen
Reporting group description:	
Three doses of 640 mg custirsen administered IV as a loading dose between Days -9 to -1. Custirsen, 640 mg, given IV weekly on Days 1, 8, and 15 of each 21 day cycle. Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day. Treatment continued for 10 cycles or until unacceptable toxicity or disease progression .	

Reporting group values	Docetaxel/prednisone	Docetaxel/prednisone/custirsen	Total
Number of subjects	512	510	1022
Age categorical Units: Subjects			
Adults (18-64 years)	156	149	305
From 65-84 years	346	359	705
85 years and over	10	2	12
Age continuous Units: years			
arithmetic mean	68.3	68.6	
standard deviation	± 7.74	± 7.75	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	512	510	1022
Race Units: Subjects			
White	461	463	924
Black or African American	14	9	23
Asian	24	28	52
American Indian or Alaska Native	2	0	2
Native Hawaiian or Pacific Islander	0	0	0
Hispanic	0	0	0
Mixed	1	1	2
Other	5	6	11
Missing	5	3	8
Ethnicity Units: Subjects			
Hispanic or Latino	28	23	51
Non-Hispanic and Non-Latino	480	485	965
Unknown	0	0	0
Missing	4	2	6
Use of Opioids for Prostate-related Cancer Pain			

This was a stratification factor.			
Units: Subjects			
Yes	171	174	345
No	341	336	677
Radiographic Evidence of Progression			
This was a stratification factor.			
Units: Subjects			
Yes	404	404	808
No	108	106	214
Weight			
Units: kg			
arithmetic mean	85.3	84.9	
standard deviation	± 16.86	± 16.7	-
Height			
Units: cm			
arithmetic mean	173.5	173.5	
standard deviation	± 7.23	± 7.69	-
Body Mass Index			
Units: kg/m^2			
arithmetic mean	28.3	28.2	
standard deviation	± 5.06	± 4.9	-
Body Surface Area			
Units: m^2			
arithmetic mean	2	2	
standard deviation	± 0.22	± 0.22	-

End points

End points reporting groups

Reporting group title	Docetaxel/prednisone

Reporting group description:

Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day.
Treatment continued for 10 cycles or until unacceptable toxicity or disease progression.

Reporting group title	Docetaxel/prednisone/custirsen

Reporting group description:

Three doses of 640 mg custirsen administered IV as a loading dose between Days -9 to -1. Custirsen, 640 mg, given IV weekly on Days 1, 8, and 15 of each 21 day cycle. Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day.
Treatment continued for 10 cycles or until unacceptable toxicity or disease progression .

Primary: Kaplan-Meier Estimates for Time to Death (Overall Survival)

End point title	Kaplan-Meier Estimates for Time to Death (Overall Survival)

End point description:

Time from the date of randomization to death from any cause. After stopping treatment, patients were followed every 4 weeks until disease progression and then followed every 12 weeks until death.

End point type	Primary

End point timeframe:

Randomization (approximately Day -12) to longest survival follow-up (Day 971).

End point values	Docetaxel/prednisone	Docetaxel/prednisone/custirsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	512[1]	510[2]		
Units: months				
median (confidence interval 95%)	22.2 (20.008 to 24.476)	23.4 (20.961 to 25.791)		

Notes:

[1] - All randomized patients

[2] - All randomized patients

Statistical analyses

Statistical analysis title	Overall Survival Analysis

Statistical analysis description:

The consequential hazard ratio used in the specific alternative hypothesis for this trial is 0.75. It was assumed that the control arm patients would have an 18-month median survival time. Under exponential assumptions, the median survival time for the investigational arm was expected to be 24 months corresponding to a hazard rate of 0.347 and a two-year survival of 50%.

Comparison groups	Docetaxel/prednisone v Docetaxel/prednisone/custirsen

Number of subjects included in analysis	1022
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.2067
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.783
upper limit	1.106

Notes:

[3] - An analysis of superiority executed as a stratified logrank test stratified by the stratification factors of 1) use of opioids for prostate-related cancer pain and 2) radiographic evidence of progression.

Secondary: Percentage of Participants Who Were Alive Without Event At Day 140

End point title	Percentage of Participants Who Were Alive Without Event At Day 140

End point description:

Patients who were alive without event (AWE) are patients who had their Milestone Day 140 Disease Status performed per protocol (Day 125 - Day 155 window), were not determined to have disease progression by the investigator on that window and confirmed as not having progressive disease (NON-PD) by the Central Imagine Lab independent review.

End point type	Secondary

End point timeframe:

Day 125-155

End point values	Docetaxel/prednisone	Docetaxel/prednisone/custirsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	512[4]	510[5]		
Units: percentage of participants				
number (not applicable)	58	57		

Notes:

[4] - All randomized patients

[5] - All randomized patients

Statistical analyses

Statistical analysis title	AWE Analysis

Statistical analysis description:

Based on Cochran-Mantel-Haenszel (CMH) Analysis with use of opioids for prostate cancer-related pain at screening (yes versus no) and radiographic evidence of progression (yes versus no) as stratification factors. P-value is not reported (NR) if Odds-Ratio (OR)<1.

Comparison groups	Docetaxel/prednisone v Docetaxel/prednisone/custirsen

Number of subjects included in analysis	1022
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.236

Other pre-specified: Percentage of Participants with Adverse Events

End point title	Percentage of Participants with Adverse Events

End point description:

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration, at any dose, of a medicinal or therapeutic product whether or not considered related to that product. Severity was rated by the investigator on a scale of 1 (mild) to 5 (death). A severity of 3 = Severe or medically significant but not immediately life-threatening. A severity of 4 = Life-threatening. Serious AEs include death (death due to progressive disease were not reported as an SAE), a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Other pre-specified

End point timeframe:

Docetaxel/prednisone/custirsen arm: Days -9 up to Day 743.
Docetaxel/prednisone arm: Day 1 up to Day 400

End point values	Docetaxel/prednisone	Docetaxel/prednisone/custirsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	499[6]	501[7]		
Units: percentage of participants				
number (not applicable)				
Any AE	97	100		
Severe AE (grade 3+)	62	77		
Serious AE	36	43		
Discontinued study early due to AE	30	43		

Notes:

[6] - Safety analysis set of participants who received at least one dose of custirsen or docetaxel.

[7] - Safety analysis set of participants who received at least one dose of custirsen or docetaxel.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Docetaxel/prednisone/custirsen arm: Days -9 up to Day 743.
Docetaxel/prednisone arm: Day 1 up to Day 400

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Docetaxel/prednisone/custirsen

Reporting group description:

Three doses of 640 mg custirsen administered IV as a loading dose between Days -9 to -1. Custirsen, 640 mg, given IV weekly on Days 1, 8, and 15 of each 21 day cycle. Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day.
Treatment continued for 10 cycles or until unacceptable toxicity or disease progression.

Reporting group title	Docetaxel/prednisone

Reporting group description:

Docetaxel (75 mg/M^2 via intravenous injection) on Day 1 of every 21 days plus prednisone (5 mg tablets taken by mouth) twice each day.
Treatment continued for 10 cycles or until unacceptable toxicity or disease progression.

Serious adverse events	Docetaxel/prednisone/custirsen	Docetaxel/prednisone	
Total subjects affected by serious adverse events			
subjects affected / exposed	214 / 501 (42.71%)	180 / 499 (36.07%)	
number of deaths (all causes)	262	267	
number of deaths resulting from adverse events	23	24	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pyogenic granuloma			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung squamous cell carcinoma stage unspecified			

subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypotension			
subjects affected / exposed	5 / 501 (1.00%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	3 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	4 / 501 (0.80%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	1 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary leak syndrome			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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			
Multi-organ failure			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Oedema peripheral			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
General physical health deterioration			

subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infusion related reaction			
subjects affected / exposed	3 / 501 (0.60%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 501 (0.20%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	16 / 501 (3.19%)	7 / 499 (1.40%)	
occurrences causally related to treatment / all	9 / 17	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	9 / 501 (1.80%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	8 / 9	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	5 / 501 (1.00%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	4 / 501 (0.80%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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			
Pneumonitis			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Epistaxis			

subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 501 (0.20%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
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	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	17 / 501 (3.39%)	16 / 499 (3.21%)	
occurrences causally related to treatment / all	9 / 17	4 / 16	
deaths causally related to treatment / all	0 / 2	0 / 1	
Dyspnoea			
subjects affected / exposed	5 / 501 (1.00%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	1 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	4 / 501 (0.80%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary aspiration			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclothymic disorder			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occult blood positive			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transaminases increased			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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			
Device occlusion			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	3 / 501 (0.60%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Femur fracture			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic agent toxicity			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple fractures			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	5 / 501 (1.00%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent occlusion			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	2 / 501 (0.40%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Myocardial infarction			

subjects affected / exposed	2 / 501 (0.40%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bradycardia			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 501 (0.40%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sick sinus syndrome			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Palpitations			

subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	8 / 501 (1.60%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	4 / 8	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 501 (0.60%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	3 / 501 (0.60%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary artery disease			

subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 501 (0.20%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 501 (0.40%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiduritis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pachymeningitis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
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 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cauda equina syndrome			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	4 / 501 (0.80%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuralgic amyotrophy			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia of malignant disease			

subjects affected / exposed	2 / 501 (0.40%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	3 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	38 / 501 (7.58%)	27 / 499 (5.41%)	
occurrences causally related to treatment / all	42 / 43	27 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	28 / 501 (5.59%)	28 / 499 (5.61%)	
occurrences causally related to treatment / all	33 / 33	30 / 31	
deaths causally related to treatment / all	1 / 1	0 / 0	
Anaemia			
subjects affected / exposed	18 / 501 (3.59%)	12 / 499 (2.40%)	
occurrences causally related to treatment / all	16 / 22	13 / 17	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	6 / 501 (1.20%)	10 / 499 (2.00%)	
occurrences causally related to treatment / all	5 / 6	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 501 (1.00%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	3 / 501 (0.60%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 501 (0.40%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	4 / 501 (0.80%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	4 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 501 (0.80%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 501 (0.00%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
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 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus paralytic			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastic ulcer			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	12 / 501 (2.40%)	9 / 499 (1.80%)	
occurrences causally related to treatment / all	11 / 12	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	12 / 501 (2.40%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	10 / 12	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	10 / 501 (2.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	4 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 501 (0.60%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colitis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis relapsing			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paptic ulcer haemorrhage			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cholecystitis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry skin			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 501 (0.40%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urinary retention			

subjects affected / exposed	2 / 501 (0.40%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 501 (0.40%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	3 / 501 (0.60%)	4 / 499 (0.80%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 1	
Haematuria			
subjects affected / exposed	4 / 501 (0.80%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesical fistula			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder mass			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 501 (0.40%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar spinal stenosis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 501 (0.60%)	5 / 499 (1.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	3 / 501 (0.60%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw disorder			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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			
Urosepsis			
subjects affected / exposed	3 / 501 (0.60%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 501 (0.40%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 501 (0.20%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 501 (0.40%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			

subjects affected / exposed	2 / 501 (0.40%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	2 / 501 (0.40%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Staphylococcal sepsis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastroenteritis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Necrotising fascitis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Endocarditis			
subjects affected / exposed	0 / 501 (0.00%)	2 / 499 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			

subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida pneumonia			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Arthritis bacterial			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	21 / 501 (4.19%)	11 / 499 (2.20%)	
occurrences causally related to treatment / all	15 / 22	7 / 12	
deaths causally related to treatment / all	3 / 3	0 / 0	
Septic shock			
subjects affected / exposed	9 / 501 (1.80%)	5 / 499 (1.00%)	
occurrences causally related to treatment / all	8 / 9	5 / 5	
deaths causally related to treatment / all	4 / 5	3 / 3	
Urinary tract infection			

subjects affected / exposed	8 / 501 (1.60%)	5 / 499 (1.00%)	
occurrences causally related to treatment / all	5 / 10	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	9 / 501 (1.80%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	4 / 9	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal osteomyelitis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia primary atypical			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal abscess			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Administration site abscess			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 501 (0.60%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	6 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 501 (0.20%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 501 (0.80%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			

subjects affected / exposed	1 / 501 (0.20%)	3 / 499 (0.60%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 501 (0.00%)	1 / 499 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	11 / 501 (2.20%)	6 / 499 (1.20%)	
occurrences causally related to treatment / all	9 / 11	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	2 / 501 (0.40%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 501 (0.20%)	0 / 499 (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	Docetaxel/prednisone/custirsen	Docetaxel/prednisone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	496 / 501 (99.00%)	476 / 499 (95.39%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	35 / 501 (6.99%)	32 / 499 (6.41%)	
occurrences (all)	42	41	
Hypotension			
subjects affected / exposed	50 / 501 (9.98%)	15 / 499 (3.01%)	
occurrences (all)	57	18	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	64 / 501 (12.77%)	61 / 499 (12.22%)	
occurrences (all)	92	89	
Fatigue			
subjects affected / exposed	241 / 501 (48.10%)	218 / 499 (43.69%)	
occurrences (all)	688	611	
Asthenia			
subjects affected / exposed	172 / 501 (34.33%)	141 / 499 (28.26%)	
occurrences (all)	393	300	
Pyrexia			
subjects affected / exposed	166 / 501 (33.13%)	68 / 499 (13.63%)	
occurrences (all)	251	102	
Oedema peripheral			

subjects affected / exposed	118 / 501 (23.55%)	94 / 499 (18.84%)	
occurrences (all)	179	132	
Chills			
subjects affected / exposed	169 / 501 (33.73%)	22 / 499 (4.41%)	
occurrences (all)	253	25	
Pain			
subjects affected / exposed	44 / 501 (8.78%)	22 / 499 (4.41%)	
occurrences (all)	55	26	
Influenza like illness			
subjects affected / exposed	33 / 501 (6.59%)	17 / 499 (3.41%)	
occurrences (all)	42	21	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	109 / 501 (21.76%)	69 / 499 (13.83%)	
occurrences (all)	157	92	
Cough			
subjects affected / exposed	106 / 501 (21.16%)	70 / 499 (14.03%)	
occurrences (all)	130	83	
Epistaxis			
subjects affected / exposed	48 / 501 (9.58%)	39 / 499 (7.82%)	
occurrences (all)	57	45	
Oropharyngeal pain			
subjects affected / exposed	28 / 501 (5.59%)	18 / 499 (3.61%)	
occurrences (all)	31	18	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	48 / 501 (9.58%)	47 / 499 (9.42%)	
occurrences (all)	55	61	
Investigations			
Weight decreased			
subjects affected / exposed	80 / 501 (15.97%)	34 / 499 (6.81%)	
occurrences (all)	117	48	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	59 / 501 (11.78%)	64 / 499 (12.83%)	
occurrences (all)	86	120	

Dysgeusia			
subjects affected / exposed	141 / 501 (28.14%)	127 / 499 (25.45%)	
occurrences (all)	224	217	
Neuropathy peripheral			
subjects affected / exposed	88 / 501 (17.56%)	90 / 499 (18.04%)	
occurrences (all)	149	139	
Dizziness			
subjects affected / exposed	81 / 501 (16.17%)	67 / 499 (13.43%)	
occurrences (all)	111	94	
Headache			
subjects affected / exposed	59 / 501 (11.78%)	47 / 499 (9.42%)	
occurrences (all)	90	73	
Paraesthesia			
subjects affected / exposed	54 / 501 (10.78%)	50 / 499 (10.02%)	
occurrences (all)	89	68	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	153 / 501 (30.54%)	89 / 499 (17.84%)	
occurrences (all)	449	255	
Anaemia			
subjects affected / exposed	155 / 501 (30.94%)	78 / 499 (15.63%)	
occurrences (all)	385	138	
Leukopenia			
subjects affected / exposed	52 / 501 (10.38%)	32 / 499 (6.41%)	
occurrences (all)	170	91	
Thrombocytopenia			
subjects affected / exposed	42 / 501 (8.38%)	10 / 499 (2.00%)	
occurrences (all)	81	20	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	55 / 501 (10.98%)	61 / 499 (12.22%)	
occurrences (all)	69	70	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	271 / 501 (54.09%)	213 / 499 (42.69%)	
occurrences (all)	614	452	
Nausea			

subjects affected / exposed	224 / 501 (44.71%)	159 / 499 (31.86%)	
occurrences (all)	390	235	
Constipation			
subjects affected / exposed	148 / 501 (29.54%)	94 / 499 (18.84%)	
occurrences (all)	205	124	
Vomiting			
subjects affected / exposed	130 / 501 (25.95%)	71 / 499 (14.23%)	
occurrences (all)	197	97	
Stomatitis			
subjects affected / exposed	57 / 501 (11.38%)	57 / 499 (11.42%)	
occurrences (all)	88	84	
Dyspepsia			
subjects affected / exposed	52 / 501 (10.38%)	46 / 499 (9.22%)	
occurrences (all)	68	60	
Abdominal pain			
subjects affected / exposed	52 / 501 (10.38%)	40 / 499 (8.02%)	
occurrences (all)	66	44	
Abdominal pain upper			
subjects affected / exposed	26 / 501 (5.19%)	21 / 499 (4.21%)	
occurrences (all)	28	23	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	209 / 501 (41.72%)	229 / 499 (45.89%)	
occurrences (all)	256	266	
Nail disorder			
subjects affected / exposed	77 / 501 (15.37%)	62 / 499 (12.42%)	
occurrences (all)	94	73	
Onycholysis			
subjects affected / exposed	27 / 501 (5.39%)	39 / 499 (7.82%)	
occurrences (all)	35	54	
Rash			
subjects affected / exposed	44 / 501 (8.78%)	22 / 499 (4.41%)	
occurrences (all)	56	30	
Dry skin			
subjects affected / exposed	24 / 501 (4.79%)	36 / 499 (7.21%)	
occurrences (all)	27	40	

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	28 / 501 (5.59%)	23 / 499 (4.61%)	
occurrences (all)	34	27	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	98 / 501 (19.56%)	85 / 499 (17.03%)	
occurrences (all)	138	119	
Arthralgia			
subjects affected / exposed	70 / 501 (13.97%)	83 / 499 (16.63%)	
occurrences (all)	111	117	
Pain in extremity			
subjects affected / exposed	66 / 501 (13.17%)	80 / 499 (16.03%)	
occurrences (all)	96	119	
Myalgia			
subjects affected / exposed	53 / 501 (10.58%)	49 / 499 (9.82%)	
occurrences (all)	117	113	
Bone pain			
subjects affected / exposed	50 / 501 (9.98%)	45 / 499 (9.02%)	
occurrences (all)	79	65	
Musculoskeletal pain			
subjects affected / exposed	48 / 501 (9.58%)	34 / 499 (6.81%)	
occurrences (all)	62	48	
Muscle spasms			
subjects affected / exposed	45 / 501 (8.98%)	28 / 499 (5.61%)	
occurrences (all)	53	33	
Muscular weakness			
subjects affected / exposed	40 / 501 (7.98%)	30 / 499 (6.01%)	
occurrences (all)	50	49	
Musculoskeletal chest pain			
subjects affected / exposed	26 / 501 (5.19%)	22 / 499 (4.41%)	
occurrences (all)	43	30	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	54 / 501 (10.78%)	51 / 499 (10.22%)	
occurrences (all)	68	61	
Nasopharyngitis			
subjects affected / exposed	36 / 501 (7.19%)	34 / 499 (6.81%)	
occurrences (all)	43	41	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	179 / 501 (35.73%)	100 / 499 (20.04%)	
occurrences (all)	300	168	
Dehydration			
subjects affected / exposed	38 / 501 (7.58%)	16 / 499 (3.21%)	
occurrences (all)	52	21	
Hypokalaemia			
subjects affected / exposed	31 / 501 (6.19%)	18 / 499 (3.61%)	
occurrences (all)	58	21	
Hyperglycaemia			
subjects affected / exposed	30 / 501 (5.99%)	13 / 499 (2.61%)	
occurrences (all)	77	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2011	The significant changes being made are as follows: • Increase the sample size of the study to 1000 patients • Modify the interim analysis to occur at 80% of the required 509 death events • Add evaluation of circulating tumor cells (CTC)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported