Clinical trial results:
A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs. Prednisone in Metastatic Castration-resistant Prostate Cancer Patients who have Received Prior Docetaxel and Prior Abiraterone or MDV3100 (COMET-1)

Summary

EudraCT number	2012-001834-33
Trial protocol	BE DE NL SE AT IE ES IT GB
Global end of trial date	25 February 2015

Results information

Result version number	v1 (current)
This version publication date	22 January 2021
First version publication date	22 January 2021

Trial information

Trial identification

Sponsor protocol code	XL184–307

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01605227
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Exelixis
Sponsor organisation address	1851 Harbor Bay Pkwy, Alameda, United States, 94502
Public contact	Exelixis Medical Affairs, Exelixis, Inc., 1 8883935494,
Scientific contact	Exelixis Medical Affairs, Exelixis, Inc., 1 8883935494,

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	07 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2014
Global end of trial reached?	Yes
Global end of trial date	25 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the effect of cabozantinib compared to prednisone on overall survival (OS) in men with previously treated metastatic castration-resistant prostate cancer with bone-dominant disease who have experienced disease progression on docetaxel-containing chemotherapy and abiraterone or MDV3100 (enzalutamide).

Protection of trial subjects:

The safety information from this study was reviewed by the Independent Data Monitoring Committee (IDMC) on a regular basis. An Exelixis internal Safety Committee met quarterly to review safety data.

Background therapy: -

Evidence for comparator:

The rationale for the use of prednisone over placebo was to offer participating subjects an active comparator which may serve to relieve pain associated with bone metastases and prolong participation in this study.

While studies with a primary endpoint of OS do not necessarily require blinding of study treatment, the use of a double-blind design, despite differential toxicity profiles between treatments, may minimize investigator bias that could affect the determination of progression and study therapy discontinuation. For this reason, prednisone plus a cabozantinib-matched placebo was chosen as the comparator regimen in this study. Subjects who received active cabozantinib also received placebo prednisone to preserve blinding. The protocol allowed prednisolone to be supplied as study treatment instead of prednisone in some countries or regions; however, only prednisone was used in this study.

Actual start date of recruitment	02 July 2012
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	United States: 156
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Puerto Rico: 1
Country: Number of subjects enrolled	Austria: 34
Country: Number of subjects enrolled	Belgium: 51
Country: Number of subjects enrolled	Germany: 125
Country: Number of subjects enrolled	Spain: 71
Country: Number of subjects enrolled	France: 212
Country: Number of subjects enrolled	United Kingdom: 85
Country: Number of subjects enrolled	Ireland: 9

Country: Number of subjects enrolled	Italy: 103
Country: Number of subjects enrolled	Netherlands: 56
Country: Number of subjects enrolled	Sweden: 37
Country: Number of subjects enrolled	Australia: 62
Worldwide total number of subjects	1028
EEA total number of subjects	698

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)	262
From 65 to 84 years	754
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 02 July 2012. Data cut-off date: 07 July 2014. A total of 1028 subjects (682 cabozantinib, 346 prednisone) were randomized to receive study treatment (ITT population).

Pre-assignment

Screening details:

Potential subjects were screened to determine if they met the required eligibility criteria. Starting with Amendment 4.0 of the protocol, subjects were permitted to be enrolled if they had radiographic evidence of liver metastasis. Qualifying screening assessments were performed within 28 days before randomization unless otherwise specified.

Pre-assignment period milestones

Number of subjects started	1028
Number of subjects completed	1028

Period 1

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

Blinding implementation details:

Cabozantinib-matched placebo was packaged and color-, size-, and shape-matched to be indistinguishable from cabozantinib.

Prednisone tablets (5 mg) were commercially obtained and overencapsulated in hard gelatin capsule shells in order to blind the product identity. Prednisone/matched placebo capsules were color- and size-matched to the overencapsulated prednisone.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Subjects randomized to the cabozantinib arm will also receive prednisone-matched placebos. Cabozantinib (XL184) 60 mg tablets are taken orally once daily and prednisone-matched placebo twice daily.

Arm type	Experimental
Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	XL184
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib tablets (60 mg) taken orally daily with prednisone-matched placebos tablets twice daily.

Arm title	Arm B

Arm description:

Subjects randomized to the prednisone/prednisolone arm will also receive placebo cabozantinib tablets. Prednisone (5 mg) is taken orally twice daily plus placebo cabozantinib tablets orally once daily.

Arm type	Experimental

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

Dosage and administration details:

Prednisone (5 mg) tablets is taken orally twice daily plus placebo cabozantinib tablets are taken orally daily.

Number of subjects in period 1	Arm A	Arm B
Started	682	346
Completed	61	17
Not completed	621	329
Clinical Deterioration	227	133
Physician decision	9	7
Consent withdrawn by subject	18	14
Adverse Event	228	42
Lost to Follow-up	1	-
Other	1	2
Progressive Disease	132	128
Sponsor Decision	2	-
Protocol Violation	1	-
No study treatment given	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Subjects randomized to the cabozantinib arm will also receive prednisone-matched placebos. Cabozantinib (XL184) 60 mg tablets are taken orally once daily and prednisone-matched placebo twice daily.	
Reporting group title	Arm B
Reporting group description:	
Subjects randomized to the prednisone/prednisolone arm will also receive placebo cabozantinib tablets. Prednisone (5 mg) is taken orally twice daily plus placebo cabozantinib tablets orally once daily.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	682	346	1028
Age categorical			
The median (range) age was 69.5 (35, 87) years in the cabozantinib arm and 69.0 (43, 89) in the prednisone arm. The majority of patients were ≥ 65 years old (76% cabozantinib; 72% prednisone), white (76% cabozantinib; 77% prednisone), and enrolled in Europe (77% cabozantinib; 74% prednisone).			
Units: Subjects			
<65	165	97	262
≥65	517	249	766
Gender categorical			
Men with previously treated docetaxel and prior abiraterone or MDV3100 (enzalutamide)			
Units: Subjects			
Female	0	0	0
Male	682	346	1028
Race Units: Subjects			
American Indian/Alaska Native	0	1	1
Asian	2	0	2
Black or African American	14	6	20
White	520	265	785
Other Race or Not Reported	146	74	220
Geographic Region Units: Subjects			
North America	119	63	182
Europe	528	256	784
Australia	35	27	62
Stratification factor: a Prior cabazitaxel (per CRF) Units: Subjects			
Yes	261	132	393
No	421	214	635
Stratification factor: a Brief Pain Inventory (BPI) Item 3 (per CRF) Units: Subjects			
< 4	389	196	585
≥ 4	284	148	432
Missing	9	2	11

Stratification factor: a ECOG performance status (per CRF) Units: Subjects			
0-1	605	303	908
=2	76	43	119
Missing	1	0	1
Opioid narcotic use within last 24 hours (per solicited opioid CRF) Units: Subjects			
Yes	454	228	682
No	228	118	346

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Subjects randomized to the cabozantinib arm will also receive prednisone-matched placebos. Cabozantinib (XL184) 60 mg tablets are taken orally once daily and prednisone-matched placebo twice daily.	
Reporting group title	Arm B
Reporting group description:	
Subjects randomized to the prednisone/prednisolone arm will also receive placebo cabozantinib tablets. Prednisone (5 mg) is taken orally twice daily plus placebo cabozantinib tablets orally once daily.	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
OS was measured from the time of randomization until 614 events, approximately 24 months after study start.	
End point type	Primary
End point timeframe:	
OS is defined as the time from randomization to death due to any cause. Participants that had not died or were permanently lost to follow-up were censored at the last known date alive. Median OS was calculated using Kaplan-Meier estimates.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	682	346		
Units: Months				
median (confidence interval 95%)	11 (10.09 to 11.63)	9.8 (9.00 to 11.53)		

Statistical analyses

Statistical analysis title	Cabozantinib, Prednisone
Statistical analysis description:	
The Intent to Treat (ITT) population was used and included 1028 randomized subjects (682 cabozantinib, 346 prednisone).	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	1028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.06

Secondary: Bone Scan Response (BSR)

End point title	Bone Scan Response (BSR)

End point description:

BSR is defined as >=30% reduction in the bone scan lesion area (BSLA) compared with baseline. Confirmation of bone scan was not required for response or progression. Bone scans were evaluated by an independent radiology facility (IRF) for response.

End point type	Secondary

End point timeframe:

BSR was measured at the end of Week 12 as determined by the Independent Radiology Review Facility (IRF).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	682	346		
Units: Percentage of Participants				
median (confidence interval 95%)	42 (38 to 46)	3 (1 to 5)		

Statistical analyses

Statistical analysis title	Cabozantinib, Prednisone

Statistical analysis description:

Analysis was conducted on the ITT population (682 cabozantinib, 346 prednisone) for Bone Scan Response (BSR) at Week 12.

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	1028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Other pre-specified: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

Duration of PFS was defined as time from the date of randomization to earlier of date of radiographic progression (bone/andor soft tissue) according to the investigator's assessment or death, assessed for up to approximately 24 months

End point type	Other pre-specified

End point timeframe:

PFS is the time from randomization to date of first documented radiographic progression (bone and/or soft tissue) according to the investigator's assessment or death. PFS was defined per mRECIST 1.1. A KM analysis was performed to estimate the median.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	682	346		
Units: Months				
median (confidence interval 95%)	5.6 (5.49 to 5.62)	2.8 (2.79 to 2.86)		

Statistical analyses

Statistical analysis title	Cabozantinib, Prednisone

Statistical analysis description:

The Intent to Treat (ITT) population was used and include 1028 randomized subjects (682 cabozantinib, 346 prednisone) with a data cut off date of 07 July 2014.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	1028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.57

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 92 weeks

Adverse event reporting additional description:

Safety was assessed based on the date of first dose and at minimum every 3 weeks up to Week 12 and every 6 weeks thereafter. The safety data includes subjects who were randomized and treated. The Safety population comprised of 1023 patients (681 cabozantinib, 342 prednisone).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Arm A

Reporting group description:

Subjects randomized to the cabozantinib arm will also receive placebo-matched prednisone capsules.

Cabozantinib (XL184) 60 mg tablets orally once daily plus prednisone-matched placebo orally twice daily.

Reporting group title	Arm B

Reporting group description:

Subjects randomized to the prednisone arm will also receive placebo-matched cabozantinib.

Prednisone 5 mg capsules orally twice daily plus cabozantinib-matched placebo orally once daily.

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	420 / 681 (61.67%)	181 / 342 (52.92%)	
number of deaths (all causes)	442	230	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 681 (0.15%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hormone-refractory prostate cancer			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	5 / 681 (0.73%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	0 / 681 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	19 / 681 (2.79%)	12 / 342 (3.51%)	
occurrences causally related to treatment / all	1 / 19	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular melanoma			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	52 / 681 (7.64%)	27 / 342 (7.89%)	
occurrences causally related to treatment / all	0 / 52	0 / 27	
deaths causally related to treatment / all	52 / 52	27 / 27	
Prostate cancer metastatic			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Second primary malignancy			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
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	11 / 681 (1.62%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	6 / 11	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	7 / 681 (1.03%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 681 (0.59%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous haemorrhage			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	18 / 681 (2.64%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	14 / 18	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 681 (0.59%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	1 / 3	1 / 1	
Device dislocation			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Euthanasia			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Fatigue			
subjects affected / exposed	20 / 681 (2.94%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	12 / 20	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	52 / 681 (7.64%)	22 / 342 (6.43%)	
occurrences causally related to treatment / all	13 / 52	3 / 22	
deaths causally related to treatment / all	0 / 9	0 / 3	
Influenza like illness			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	5 / 681 (0.73%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	8 / 681 (1.17%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	2 / 681 (0.29%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Non-cardiac chest pain			
subjects affected / exposed	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	3 / 681 (0.44%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	10 / 681 (1.47%)	7 / 342 (2.05%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	15 / 681 (2.20%)	6 / 342 (1.75%)	
occurrences causally related to treatment / all	2 / 15	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile swelling			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal pain			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal swelling			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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			

Acute respiratory failure			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	10 / 681 (1.47%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	3 / 10	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	5 / 681 (0.73%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	9 / 681 (1.32%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	4 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	4 / 681 (0.59%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	42 / 681 (6.17%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	26 / 42	2 / 3	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 681 (0.44%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	7 / 681 (1.03%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			

subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium test positive			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 681 (0.15%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell count decreased			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratorhexis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy complication			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cystic lymphangioma			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic myopathy			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	5 / 681 (0.73%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	5 / 681 (0.73%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure			
subjects affected / exposed	4 / 681 (0.59%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			

subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stress cardiomyopathy			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	4 / 681 (0.59%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cognitive disorder			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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 / 681 (0.15%)	0 / 342 (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	2 / 681 (0.29%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 681 (0.15%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	3 / 681 (0.44%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 681 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 681 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensorimotor disorder			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory loss			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	14 / 681 (2.06%)	8 / 342 (2.34%)	
occurrences causally related to treatment / all	1 / 14	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord paralysis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stupor			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 681 (0.73%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 681 (4.70%)	16 / 342 (4.68%)	
occurrences causally related to treatment / all	10 / 32	5 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 681 (0.44%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 681 (0.29%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	6 / 681 (0.88%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	2 / 6	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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 distension			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	8 / 681 (1.17%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	4 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 681 (0.15%)	9 / 342 (2.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			
subjects affected / exposed	12 / 681 (1.76%)	6 / 342 (1.75%)	
occurrences causally related to treatment / all	5 / 12	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	10 / 681 (1.47%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	9 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 681 (0.44%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			

subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestine perforation			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	23 / 681 (3.38%)	6 / 342 (1.75%)	
occurrences causally related to treatment / all	20 / 23	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	28 / 681 (4.11%)	6 / 342 (1.75%)	
occurrences causally related to treatment / all	19 / 28	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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			
Angioedema			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stasis dermatitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder dysfunction			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder outlet obstruction			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	5 / 681 (0.73%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	5 / 681 (0.73%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydroureter			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 681 (0.29%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 1	
Renal failure acute			
subjects affected / exposed	12 / 681 (1.76%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	5 / 12	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	7 / 681 (1.03%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	4 / 681 (0.59%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cushing's syndrome			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaldosteronism			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 681 (0.88%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	1 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	14 / 681 (2.06%)	8 / 342 (2.34%)	
occurrences causally related to treatment / all	0 / 14	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	15 / 681 (2.20%)	11 / 342 (3.22%)	
occurrences causally related to treatment / all	0 / 15	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
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	4 / 681 (0.59%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	3 / 681 (0.44%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 681 (0.15%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			

subjects affected / exposed	3 / 681 (0.44%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	4 / 681 (0.59%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	5 / 681 (0.73%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	4 / 681 (0.59%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	4 / 681 (0.59%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 681 (0.15%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			

subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 681 (0.44%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 681 (0.29%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	5 / 681 (0.73%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	17 / 681 (2.50%)	12 / 342 (3.51%)	
occurrences causally related to treatment / all	0 / 17	0 / 12	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pneumonia klebsiella			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	2 / 681 (0.29%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulpitis dental			

subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	11 / 681 (1.62%)	5 / 342 (1.46%)	
occurrences causally related to treatment / all	1 / 11	1 / 5	
deaths causally related to treatment / all	0 / 3	0 / 2	
Septic shock			
subjects affected / exposed	3 / 681 (0.44%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 2	1 / 1	
Sinusitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	1 / 681 (0.15%)	5 / 342 (1.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	13 / 681 (1.91%)	6 / 342 (1.75%)	
occurrences causally related to treatment / all	2 / 13	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	7 / 681 (1.03%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uncoded: NOCARDIA SEPSIS	Additional description: Uncoded		

subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (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			
Cachexia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	15 / 681 (2.20%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	10 / 15	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	20 / 681 (2.94%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	13 / 20	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 681 (0.15%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	2 / 681 (0.29%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	1 / 681 (0.15%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	5 / 681 (0.73%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	7 / 681 (1.03%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	4 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	3 / 681 (0.44%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 681 (0.15%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	675 / 681 (99.12%)	332 / 342 (97.08%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	191 / 681 (28.05%)	38 / 342 (11.11%)	
occurrences (all)	191	38	
Hypotension			
subjects affected / exposed	36 / 681 (5.29%)	13 / 342 (3.80%)	
occurrences (all)	36	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	228 / 681 (33.48%)	63 / 342 (18.42%)	
occurrences (all)	228	63	
Fatigue			
subjects affected / exposed	338 / 681 (49.63%)	119 / 342 (34.80%)	
occurrences (all)	338	119	
General physical health deterioration			
subjects affected / exposed	47 / 681 (6.90%)	13 / 342 (3.80%)	
occurrences (all)	47	13	
Mucosal inflammation			
subjects affected / exposed	134 / 681 (19.68%)	9 / 342 (2.63%)	
occurrences (all)	134	9	
Oedema peripheral			
subjects affected / exposed	101 / 681 (14.83%)	43 / 342 (12.57%)	
occurrences (all)	101	43	
Pain			
subjects affected / exposed	56 / 681 (8.22%)	33 / 342 (9.65%)	
occurrences (all)	56	33	
Pyrexia			
subjects affected / exposed	67 / 681 (9.84%)	36 / 342 (10.53%)	
occurrences (all)	67	36	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	52 / 681 (7.64%)	15 / 342 (4.39%)	
occurrences (all)	52	15	
Dysphonia			
subjects affected / exposed	180 / 681 (26.43%)	21 / 342 (6.14%)	
occurrences (all)	180	21	
Dyspnoea			
subjects affected / exposed	135 / 681 (19.82%)	46 / 342 (13.45%)	
occurrences (all)	135	46	
Epistaxis			
subjects affected / exposed	37 / 681 (5.43%)	9 / 342 (2.63%)	
occurrences (all)	37	9	
Psychiatric disorders			
Depression			
subjects affected / exposed	42 / 681 (6.17%)	11 / 342 (3.22%)	
occurrences (all)	42	11	
Insomnia			
subjects affected / exposed	53 / 681 (7.78%)	28 / 342 (8.19%)	
occurrences (all)	53	28	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	56 / 681 (8.22%)	10 / 342 (2.92%)	
occurrences (all)	56	10	
Aspartate aminotransferase increased			
subjects affected / exposed	70 / 681 (10.28%)	14 / 342 (4.09%)	
occurrences (all)	70	14	
Weight decreased			
subjects affected / exposed	237 / 681 (34.80%)	41 / 342 (11.99%)	
occurrences (all)	237	41	
Nervous system disorders			
Dizziness			
subjects affected / exposed	48 / 681 (7.05%)	19 / 342 (5.56%)	
occurrences (all)	48	19	
Dysgeusia			
subjects affected / exposed	175 / 681 (25.70%)	16 / 342 (4.68%)	
occurrences (all)	175	16	

Headache			
subjects affected / exposed	87 / 681 (12.78%)	14 / 342 (4.09%)	
occurrences (all)	87	14	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	203 / 681 (29.81%)	111 / 342 (32.46%)	
occurrences (all)	203	111	
Thrombocytopenia			
subjects affected / exposed	42 / 681 (6.17%)	20 / 342 (5.85%)	
occurrences (all)	42	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	76 / 681 (11.16%)	16 / 342 (4.68%)	
occurrences (all)	76	16	
Abdominal pain upper			
subjects affected / exposed	43 / 681 (6.31%)	16 / 342 (4.68%)	
occurrences (all)	43	16	
Constipation			
subjects affected / exposed	227 / 681 (33.33%)	100 / 342 (29.24%)	
occurrences (all)	227	100	
Diarrhoea			
subjects affected / exposed	349 / 681 (51.25%)	68 / 342 (19.88%)	
occurrences (all)	349	68	
Dry mouth			
subjects affected / exposed	65 / 681 (9.54%)	11 / 342 (3.22%)	
occurrences (all)	65	11	
Dyspepsia			
subjects affected / exposed	58 / 681 (8.52%)	6 / 342 (1.75%)	
occurrences (all)	58	6	
Dysphagia			
subjects affected / exposed	41 / 681 (6.02%)	0 / 342 (0.00%)	
occurrences (all)	41	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	37 / 681 (5.43%)	7 / 342 (2.05%)	
occurrences (all)	37	7	
Nausea			

subjects affected / exposed	390 / 681 (57.27%)	102 / 342 (29.82%)	
occurrences (all)	390	102	
Stomatitis			
subjects affected / exposed	127 / 681 (18.65%)	9 / 342 (2.63%)	
occurrences (all)	127	8	
Vomiting			
subjects affected / exposed	271 / 681 (39.79%)	67 / 342 (19.59%)	
occurrences (all)	271	67	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	53 / 681 (7.78%)	8 / 342 (2.34%)	
occurrences (all)	53	8	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	200 / 681 (29.37%)	5 / 342 (1.46%)	
occurrences (all)	200	5	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	94 / 681 (13.80%)	1 / 342 (0.29%)	
occurrences (all)	94	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	91 / 681 (13.36%)	50 / 342 (14.62%)	
occurrences (all)	91	50	
Back pain			
subjects affected / exposed	115 / 681 (16.89%)	64 / 342 (18.71%)	
occurrences (all)	115	64	
Bone pain			
subjects affected / exposed	109 / 681 (16.01%)	63 / 342 (18.42%)	
occurrences (all)	109	63	
Muscle spasms			
subjects affected / exposed	48 / 681 (7.05%)	20 / 342 (5.85%)	
occurrences (all)	48	20	
Muscular weakness			
subjects affected / exposed	48 / 681 (7.05%)	22 / 342 (6.43%)	
occurrences (all)	48	22	
Musculoskeletal pain			

subjects affected / exposed	43 / 681 (6.31%)	37 / 342 (10.82%)	
occurrences (all)	43	37	
Pain in extremity			
subjects affected / exposed	98 / 681 (14.39%)	36 / 342 (10.53%)	
occurrences (all)	98	36	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	71 / 681 (10.43%)	29 / 342 (8.48%)	
occurrences (all)	71	29	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	407 / 681 (59.77%)	99 / 342 (28.95%)	
occurrences (all)	407	99	
Dehydration			
subjects affected / exposed	38 / 681 (5.58%)	15 / 342 (4.39%)	
occurrences (all)	38	15	
Hypocalcaemia			
subjects affected / exposed	50 / 681 (7.34%)	20 / 342 (5.85%)	
occurrences (all)	50	20	
Hypokalaemia			
subjects affected / exposed	69 / 681 (10.13%)	9 / 342 (2.63%)	
occurrences (all)	69	9	
Hypomagnesaemia			
subjects affected / exposed	36 / 681 (5.29%)	3 / 342 (0.88%)	
occurrences (all)	36	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2012	Protocol Amendment 1.0
21 March 2012	Protocol Amendment 2.0
18 May 2012	Protocol Amendment 3.0
18 June 2012	Protocol Amendment 4.0
23 August 2012	Protocol Amendment 4.1 (France)
18 July 2013	Protocol Amendment 5.0
18 July 2013	Protocol Amendment 5.1 (France)
16 July 2014	Protocol Amendment 6.0
16 July 2014	Protocol Amendment 6.1 (France)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 September 2014	Information Amendment: Clinical (Notification of XL184-307 Discontinuation) to FDA (US)	-

Notes:

Limitations and caveats

None reported