



Clinical trial results:

A randomised, open-label phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC

Summary

EudraCT number	2013-003156-21
Trial protocol	BE IT IE DE GB AT ES SI PL
Global end of trial date	29 February 2020

Results information

Result version number	v1 (current)
This version publication date	25 September 2021
First version publication date	25 September 2021

Trial information

Trial identification

Sponsor protocol code	ETOP_5-12/EORTC_08111
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02129699
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen number: 20080166

Notes:

Sponsors

Sponsor organisation name	European Thoracic Oncology Platform
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	ETOP Coordinating Office, ETOP , +41 31389 93 91, SPLENDOR@etop-eu.org
Scientific contact	ETOP Coordinating Office, ETOP , +41 31389 93 91, SPLENDOR@etop-eu.org

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	01 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2018
Global end of trial reached?	Yes
Global end of trial date	29 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether the addition of denosumab to standard firstline chemotherapy in advanced NSCLC improves overall survival.

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at <http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf>). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

All patients will receive standard, platinum-based doublet chemotherapy combined with pemetrexed or gemcitabine for first-line NSCLC. The number of cycles of doublet chemotherapy will be between 4 and 6 cycles, according to the institution's policy. Similarly, pemetrexed or erlotinib maintenance treatment after doublet chemotherapy is allowed in both arms.

Evidence for comparator:

Denosumab is a fully human monoclonal IgG2 antibody binding with a high affinity to RANKL. It is specific and does not demonstrate significant binding to other members of the TNF ligand superfamily. As a result of its specific mechanism of action on the bone matrix, denosumab has become a new option for the treatment of osteoporosis [Aeschlimann et al Cell Death Differ 2004]. In breast cancer, denosumab was demonstrated superior to zoledronic acid in delaying time to first on-study SRE (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; P = .01 superiority), associated with a greater reduction in bone turnover markers. Overall survival, disease progression, and rates of adverse events were similar between groups [Stopeck et al J Clin Oncol 2010].

In a pivotal phase 3 trial in patients with solid tumours and multiple myeloma (other than breast or prostate) and bone metastasis, denosumab was shown to be non-inferior – with a trend toward superiority – to zoledronic acid in delaying time to first SRE (HR, 0.84; 95% CI, 0.71 to 0.98; P= .0007, representing 16% reduction in hazard). Regarding NSCLC, the effect of denosumab on time to first on-study SRE relative to zoledronic acid by tumour stratification factors resulted in an HR of 0.84 for NSCLC (95% CI, 0.64 to 1.10; P=0.20) [Henry et al. J Clin Oncol 2011].

Actual start date of recruitment	01 August 2014
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	Poland: 13
Country: Number of subjects enrolled	Slovenia: 158

Country: Number of subjects enrolled	Spain: 98
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 55
Country: Number of subjects enrolled	France: 65
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Ireland: 33
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	514
EEA total number of subjects	514

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)	224
From 65 to 84 years	290
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on Jan 12, 2015. On Jan 31, 2018, when accrual to the study was closed, 595 patients were registered in the study by 55 sites in 10 countries. Of the 595 patients who were screened and registered, 514 (86%) were randomized.

Pre-assignment

Screening details:

Age \geq 18 years

ECOG performance status 0-2

Histologically or cytologically confirmed advanced stage IV non-small cell lung carcinoma (NSCLC), according to 7th TNM classification

Life expectancy of at least 3 months.

Pre-assignment period milestones

Number of subjects started	514
Number of subjects completed	514

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemotherapy

Arm description:

Patients diagnosed with advanced NSCLC who were randomized to receive doublet chemotherapy + best supportive care

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

Dosage and administration details:

Patients in the chemotherapy arm will receive 4 – 6 cycles of one of the above combinations + best supportive care;-

CisPem: cisplatin 75 mg/m², i.v. day 1, plus pemetrexed 500 mg/m² i.v. day 1

CarboPem: carboplatin AUC 5, i.v. day 1, plus pemetrexed 500 mg/m² i.v. day 1

Arm title	Chemotherapy + Denosumab
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Arm description:

4 – 6 cycles of doublet chemotherapy + denosumab 120 mg, s.c. every 3-4 weeks until unacceptable toxicity, patient refusal or patient's death. Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient. In cycle 1, an additional dose will be given on day 8.

Arm type	Experimental
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Investigational medicinal product name	Chemotherapy + Denosumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

4 – 6 cycles of doublet chemotherapy + denosumab 120 mg, subcutaneous (s.c). every 3-4 weeks until unacceptable toxicity, patient refusal or patient's death. Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient. In cycle 1, an additional dose will be given on day 8.

Number of subjects in period 1	Chemotherapy	Chemotherapy + Denosumab
Started	255	259
Completed	252	257
Not completed	3	2
Did not start treatment	3	2

Baseline characteristics

Reporting groups

Reporting group title	Chemotherapy
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Reporting group description:

Patients diagnosed with advanced NSCLC who were randomized to receive doublet chemotherapy + best supportive care

Reporting group title	Chemotherapy + Denosumab
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Reporting group description:

4 – 6 cycles of doublet chemotherapy + denosumab 120 mg, s.c. every 3-4 weeks until unacceptable toxicity, patient refusal or patient's death. Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient. In cycle 1, an additional dose will be given on day 8.

Reporting group values	Chemotherapy	Chemotherapy + Denosumab	Total
Number of subjects	255	259	514
Age categorical			
Units: Subjects			
Adults (18-64 years)	117	107	224
From 65-84 years	138	152	290
Gender categorical			
Units: Subjects			
Female	187	179	366
Male	68	80	148
Histology			
Stratification factor			
Units: Subjects			
Squamous	65	70	135
Non-squamous	187	183	370
Mixed	3	6	9
Bone metastasis			
Stratification factor			
Units: Subjects			
No	118	121	239
Yes	137	138	275
ECOG PS			
Stratification factor			
Units: Subjects			
PS 0/1	229	230	459
PS 2	26	29	55
Region			
Stratification factor			
Units: Subjects			
Eastern Europe	18	10	28
Western Europe	153	162	315
Southern Europe	84	87	171

End points

End points reporting groups

Reporting group title	Chemotherapy
Reporting group description:	
Patients diagnosed with advanced NSCLC who were randomized to receive doublet chemotherapy + best supportive care	
Reporting group title	Chemotherapy + Denosumab
Reporting group description:	
4 – 6 cycles of doublet chemotherapy + denosumab 120 mg, s.c. every 3-4 weeks until unacceptable toxicity, patient refusal or patient's death. Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient. In cycle 1, an additional dose will be given on day 8.	

Primary: Overall survival

End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe:	
Defined as time from the date of randomisation until death from any cause. Patients who are still alive at last contact are censored at the date of last follow up.	

End point values	Chemotherapy	Chemotherapy + Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	259		
Units: Years				
median (confidence interval 95%)	0.73 (0.63 to 0.92)	0.68 (0.62 to 0.87)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Cox regression model for treatment effect, analysis adjusted for stratification factors	
Comparison groups	Chemotherapy v Chemotherapy + Denosumab
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.355
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.19

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
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End point description:

All survival estimates and statistical analyses reported for that endpoint are done on the Intention-to-Treat

(ITT) population: all eligible patients that were randomized treatment.

End point type	Secondary
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End point timeframe:

Progression-free survival (PFS) is defined as time from date of randomisation until objective disease progression or death, whichever occurs first. If neither event has been observed, then the patient is censored at the date of the last follow up.

End point values	Chemotherapy	Chemotherapy + Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	259		
Units: % at 1 Year				
number (confidence interval 95%)	9.3 (5.9 to 13.5)	13.1 (9.1 to 17.9)		

Statistical analyses

Statistical analysis title	Secondary analysis
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Statistical analysis description:

This analysis is applied on the Intention to treat (ITT) population, with the secondary endpoint of PFS this time. Cox regression was used to compare the experimental versus the standard (control) arm, adjusted for stratification factors used at randomization, with a 1-sided Wald test.

Comparison groups	Chemotherapy + Denosumab v Chemotherapy
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.459
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.19

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on a CRF to be submitted at pre-specified timepoint: during first-line platinum based doublet chemotherapy (chemo + SOC) and after stop of first-line platinum based doublet chemotherapy until end of trial (chemo + denosumab)

Adverse event reporting additional description:

Reproting of AEs and SAEs are done according to NCI CTCAE v 4.0

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Chemo + SOC
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Reporting group description: -

Reporting group title	Chemo + Denosumab
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Reporting group description: -

Serious adverse events	Chemo + SOC	Chemo + Denosumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	97 / 255 (38.04%)	138 / 259 (53.28%)	
number of deaths (all causes)	178	177	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CANCER PAIN			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCRINE NEOPLASM MALIGNANT			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
LYMPHANGIOSIS CARCINOMATOSA			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
METASTASES TO CENTRAL NERVOUS SYSTEM			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RECTAL ADENOCARCINOMA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR ASSOCIATED FEVER			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
HYPERTENSION			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ISCHAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 255 (1.18%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	3 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONDITION AGGRAVATED			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 5	
DISEASE PROGRESSION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
EUTHANASIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
FATIGUE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 255 (2.35%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	6 / 6	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 255 (1.96%)	6 / 259 (2.32%)	
occurrences causally related to treatment / all	3 / 5	1 / 7	
deaths causally related to treatment / all	1 / 1	0 / 1	
HYPERTHERMIA			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 255 (1.18%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
PAIN			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 255 (1.18%)	7 / 259 (2.70%)	
occurrences causally related to treatment / all	1 / 3	0 / 7	
deaths causally related to treatment / all	1 / 1	0 / 0	
PYREXIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 255 (1.96%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	4 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
HYPERSENSITIVITY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ACUTE RESPIRATORY FAILURE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
BRONCHOSPASM			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSпноEA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 255 (0.78%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGOBRONCHIAL FISTULA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
PNEUMONITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

PULMONARY EMBOLISM alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 4 / 255 (1.57%) 2 / 4 0 / 0	 3 / 259 (1.16%) 0 / 3 0 / 2	
PULMONARY OEDEMA alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 255 (0.00%) 0 / 0 0 / 0	 1 / 259 (0.39%) 0 / 1 0 / 1	
RESPIRATORY FAILURE alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 255 (0.78%) 0 / 2 0 / 1	 2 / 259 (0.77%) 1 / 2 1 / 2	
Psychiatric disorders COMPLETED SUICIDE alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 255 (0.39%) 0 / 1 0 / 1	 0 / 259 (0.00%) 0 / 0 0 / 0	
CONFUSIONAL STATE alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 255 (0.39%) 0 / 1 0 / 0	 2 / 259 (0.77%) 0 / 2 0 / 0	
DEPRESSION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 255 (0.39%) 0 / 1 0 / 0	 0 / 259 (0.00%) 0 / 0 0 / 0	
SUICIDE ATTEMPT alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OXYGEN SATURATION DECREASED			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
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			
ANAL INJURY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT DISLOCATION			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
APLASIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIAC FAILURE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 2	
CARDIAC FAILURE CONGESTIVE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOGENIC SHOCK			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIOPULMONARY FAILURE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIO-RESPIRATORY ARREST			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CORONARY ARTERY INSUFFICIENCY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

MYOCARDIAL INFARCTION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 255 (0.78%) 0 / 2 0 / 0	2 / 259 (0.77%) 0 / 2 0 / 1	
Nervous system disorders CAROTID ARTERY OCCLUSION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 1 / 1 1 / 1	0 / 259 (0.00%) 0 / 0 0 / 0	
CEREBRAL INFARCTION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0	
CEREBRAL ISCHAEMIA alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0	
CEREBRAL VENOUS SINUS THROMBOSIS alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0	
CEREBROVASCULAR ACCIDENT alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 3 0 / 1	
DIZZINESS alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEADACHE alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOAESTHESIA alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROLOGICAL DECOMPENSATION alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
PERONEAL NERVE PALSY alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SYNCOPE alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 0 / 1 0 / 0	3 / 259 (1.16%) 1 / 3 0 / 0	
TRANSIENT ISCHAEMIC ATTACK alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0	
Blood and lymphatic system disorders			
ANAEMIA alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	14 / 255 (5.49%) 16 / 16 0 / 0	9 / 259 (3.47%) 10 / 11 0 / 0	
ANAEMIA OF MALIGNANT DISEASE alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 1 / 1 0 / 0	
FEBRILE BONE MARROW APLASIA alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 1 / 1 0 / 0	
FEBRILE NEUTROPENIA alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 255 (1.18%) 1 / 3 0 / 0	10 / 259 (3.86%) 8 / 11 2 / 2	
HAEMATOTOXICITY alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 255 (3.53%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	9 / 10	7 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
NORMOCYTIC ANAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 255 (1.96%)	10 / 259 (3.86%)	
occurrences causally related to treatment / all	5 / 5	11 / 12	
deaths causally related to treatment / all	2 / 2	1 / 1	
SPLENIC HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 255 (3.53%)	13 / 259 (5.02%)	
occurrences causally related to treatment / all	9 / 10	13 / 14	
deaths causally related to treatment / all	0 / 0	1 / 1	

Ear and labyrinth disorders VERTIGO alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 0 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0	
VERTIGO POSITIONAL alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0	
Gastrointestinal disorders ABDOMINAL PAIN alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 1 / 1 0 / 0	2 / 259 (0.77%) 0 / 2 0 / 0	
ABDOMINAL PAIN UPPER alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	3 / 259 (1.16%) 0 / 3 0 / 0	
ANAL HAEMORRHAGE alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0	
ASCITES alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 1 / 1 0 / 0	
COLITIS alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 255 (2.75%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	5 / 7	5 / 8	
deaths causally related to treatment / all	1 / 1	0 / 0	
DYSPHAGIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

GASTROINTESTINAL INFLAMMATION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 1 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
GINGIVAL DISORDER alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 1 / 1 0 / 0		
ILEUS alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 0 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
IMMUNE-MEDIATED ENTEROCOLITIS alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0		
NAUSEA alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	6 / 255 (2.35%) 8 / 8 0 / 0	15 / 259 (5.79%) 15 / 19 0 / 0		
NEUTROPENIC COLITIS alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 1 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
ODYNOPHAGIA alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL STENOSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 255 (1.18%)	11 / 259 (4.25%)	
occurrences causally related to treatment / all	4 / 4	11 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FUNCTION ABNORMAL			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DRUG ERUPTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULAR			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC EPIDERMAL NECROLYSIS			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 255 (1.57%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	2 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC KIDNEY DISEASE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
RENAL FAILURE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 255 (2.35%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	5 / 7	0 / 4	
deaths causally related to treatment / all	2 / 2	0 / 1	
URINARY RETENTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT OBSTRUCTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (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			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHONDROCALCINOSIS PYROPHOSPHATE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
APPENDICITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL SEPSIS			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
BRONCHITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE OCCLUSION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROBACTER INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

FEBRILE INFECTION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 0		
FUNGAL INFECTION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 0 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
GASTROENTERITIS VIRAL alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 0 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
HERPES SIMPLEX OESOPHAGITIS alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 1 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
INFECTION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 1 / 1 0 / 0	1 / 259 (0.39%) 1 / 1 1 / 1		
INFLUENZA alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	2 / 259 (0.77%) 0 / 2 0 / 0		
LOWER RESPIRATORY TRACT INFECTION alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	3 / 255 (1.18%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECROTISING FASCIITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEUTROPENIC SEPSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
OESOPHAGEAL CANDIDIASIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAROTITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PICORNAVIRUS INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 255 (3.53%)	17 / 259 (6.56%)	
occurrences causally related to treatment / all	3 / 9	3 / 17	
deaths causally related to treatment / all	1 / 3	0 / 2	

PNEUMONIA NECROTISING alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 255 (0.00%) 0 / 0 0 / 0	1 / 259 (0.39%) 0 / 1 0 / 1		
PNEUMONIA STAPHYLOCOCCAL alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 0 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
PSEUDOMONAL SEPSIS alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 255 (0.39%) 1 / 1 0 / 0	0 / 259 (0.00%) 0 / 0 0 / 0		
RESPIRATORY TRACT INFECTION alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	9 / 255 (3.53%) 3 / 9 0 / 0	4 / 259 (1.54%) 1 / 4 0 / 0		
SEPSIS alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 255 (1.57%) 0 / 4 0 / 3	6 / 259 (2.32%) 2 / 7 2 / 3		
SEPTIC SHOCK alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 255 (1.18%) 2 / 3 2 / 3	5 / 259 (1.93%) 1 / 5 0 / 1		
STAPHYLOCOCCAL SEPSIS alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRACHEOBRONCHITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 255 (1.96%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
UROSEPSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 255 (2.35%)	6 / 259 (2.32%)	
occurrences causally related to treatment / all	6 / 6	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 255 (0.78%)	7 / 259 (2.70%)	
occurrences causally related to treatment / all	0 / 2	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 255 (0.39%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 255 (1.18%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	

HYPOPHOSPHATAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 255 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Chemo + SOC	Chemo + Denosumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	235 / 255 (92.16%)	246 / 259 (94.98%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOPATHY			
alternative dictionary used: NCI- CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
BRAIN METASTASES			
alternative dictionary used: NCI- CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
SEEPING METASTASIS UNDER SKIN			
alternative dictionary used: NCI- CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
TENDERNESS AT SITE OF LUNG MASS			
alternative dictionary used: NCI- CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
TUMOR PAIN			
alternative dictionary used: NCI- CTCAE 4.0			
subjects affected / exposed	6 / 255 (2.35%)	7 / 259 (2.70%)	
occurrences (all)	8	7	
Vascular disorders			

ARTERIAL HYPERTENSION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
HEMATOMA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	3 / 259 (1.16%)
occurrences (all)	3	4
HOT FLASHES		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	6 / 259 (2.32%)
occurrences (all)	2	6
HOT FLASHES - RIGHT ARM		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HYPERTENSION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	96 / 255 (37.65%)	109 / 259 (42.08%)
occurrences (all)	218	326
HYPERTENTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HYPOTENSION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	6 / 255 (2.35%)	9 / 259 (3.47%)
occurrences (all)	6	10
LYMPH LEAKAGE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
LYMPHEDEMA		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	2
PERIPHERAL ISCHEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)
occurrences (all)	5	0
PHLEBITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	2 / 259 (0.77%)
occurrences (all)	4	2
RAYNAUD		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RAYNAUD'S DISEASE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
RENAL INFARCTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
THROMBOEMBOLIC EVENT		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	13 / 255 (5.10%)	14 / 259 (5.41%)
occurrences (all)	15	16
VASCULAR DISORDERS - OTHER, SPECIFY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
VASCULAR SCLEROSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0

<p>VASCULITIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>Surgical and medical procedures</p> <p>PAIN STENT</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PLEURX</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>TOOTH EXTRACTION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p> <p>0 / 255 (0.00%)</p> <p>0</p> <p>0 / 255 (0.00%)</p> <p>0</p> <p>0 / 255 (0.00%)</p> <p>0</p>	<p>0 / 259 (0.00%)</p> <p>0</p> <p>1 / 259 (0.39%)</p> <p>1</p> <p>1 / 259 (0.39%)</p> <p>1</p>	
<p>General disorders and administration site conditions</p> <p>ALTERATION OF GENERAL CONDITION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ALTERATION OF GENERAL STATUS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BACK PAIN</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BONE PAIN</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>2</p> <p>0 / 255 (0.00%)</p> <p>0</p> <p>1 / 255 (0.39%)</p> <p>1</p> <p>0 / 255 (0.00%)</p> <p>0</p>	<p>0 / 259 (0.00%)</p> <p>0</p> <p>1 / 259 (0.39%)</p> <p>1</p> <p>0 / 259 (0.00%)</p> <p>0</p> <p>1 / 259 (0.39%)</p> <p>1</p>	

CHEST WALL PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
CHILLS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	5 / 259 (1.93%)
occurrences (all)	0	6
CONSTITUTIONAL SYNDROME		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	2	0
CRAMPS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DEATH NOS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
DECLINE IN GENERAL HEALTH STATUS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
DECLINE IN HEALTH STATUS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
DECREASED MOBILITY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
DETERIORATION IN HEALTH		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DETERIORATION OF GENERAL STATE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
DRY MUCOSAE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DRY MUCOUS MEMBRANES		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
EDEMA FACE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
EDEMA LIMBS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	31 / 255 (12.16%)	27 / 259 (10.42%)
occurrences (all)	43	37
FACIAL PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	3 / 259 (1.16%)
occurrences (all)	0	3
FATIGUE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	120 / 255 (47.06%)	133 / 259 (51.35%)
occurrences (all)	214	287
FEVER		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	22 / 255 (8.63%)	21 / 259 (8.11%)
occurrences (all)	23	30

FLU LIKE SYMPTOMS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	7 / 255 (2.75%)	5 / 259 (1.93%)
occurrences (all)	9	6
GAIT DISTURBANCE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1
GENERAL DETERIORATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	2 / 259 (0.77%)
occurrences (all)	3	3
GENERAL DISORDERS + ADMINISTRATION SITE CONDITIONS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	2	1
GENERAL HEALTH DETERIORATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
GENERAL PHYSICAL HEALTH DETERIORATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
GENERALIZED EDEMA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HEADACHE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HEALTH DETERIORATION		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
HOT FLASHES DURING THE NIGHT		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
INFUSION SITE EXTRAVASATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
INJECTION SITE REACTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1
IRRITABILITY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
LOCALIZED EDEMA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	5 / 259 (1.93%)
occurrences (all)	3	6
LOSS OF APPETITE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
MALAISE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	12 / 255 (4.71%)	19 / 259 (7.34%)
occurrences (all)	16	23
MULTI-ORGAN FAILURE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1

NIGHT SWEATS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	1 / 259 (0.39%)
occurrences (all)	3	1
NON CARDIAC CHEST PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	2
NON-CARDIAC CHEST PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	15 / 255 (5.88%)	21 / 259 (8.11%)
occurrences (all)	18	24
PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	33 / 255 (12.94%)	33 / 259 (12.74%)
occurrences (all)	50	55
PAIN IN EXTREMITY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
'PAIN IN EXTREMITY'		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PAIN OTHER - LEFT GROIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PROGRESSION OF DISEASE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	2	0
SUBFEBRILE TEMPERATURES		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
SUDDEN DEATH NOS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
SWEAT			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
SWOLLEN FACE			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
WORSENING OF CLINICAL CONDITION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
WORSENING OF GENERAL CONDITION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)	
occurrences (all)	1	2	
Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	5 / 255 (1.96%)	5 / 259 (1.93%)	
occurrences (all)	5	5	
INTOLERANCE OF RED BLOOD CELL CONCENTRATE			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
RIGHT CERVICAL LYMPHADENOPATHY			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed occurrences (all)	1 / 255 (0.39%) 1	0 / 259 (0.00%) 0	
Reproductive system and breast disorders			
BREAST PAIN alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
DYSMENORRHEA alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
ERECTILE DYSFUNCTION alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	2 / 259 (0.77%) 2	
PELVIC PAIN alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
PENILE PAIN alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	2 / 255 (0.78%) 2	0 / 259 (0.00%) 0	
VAGINAL DRYNESS alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
Respiratory, thoracic and mediastinal disorders			
ADULT RESPIRATORY DISTRESS SYNDROME alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 255 (0.39%) 2	0 / 259 (0.00%) 0	
ALLERGIC RHINITIS alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	1 / 255 (0.39%)	4 / 259 (1.54%)
occurrences (all)	1	4
ATELECTASIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	3 / 259 (1.16%)
occurrences (all)	2	6
BRONCHIAL OBSTRUCTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
BRONCHIAL STRICTURE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
BRONCHOPULMONARY HEMORRHAGE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	2	0
BRONCHOPULMONARY HEMORRHAGE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	13 / 259 (5.02%)
occurrences (all)	5	18
BRONCHOSPASM		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
COUGH		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	33 / 255 (12.94%)	56 / 259 (21.62%)
occurrences (all)	43	81
DYSPNEA		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	62 / 255 (24.31%)	72 / 259 (27.80%)
occurrences (all)	80	108
EMPHYSEMA LUNG		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
EPISTAXIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	16 / 255 (6.27%)	11 / 259 (4.25%)
occurrences (all)	18	11
HEMOPTYSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)
occurrences (all)	0	2
HICCUPS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	5 / 259 (1.93%)
occurrences (all)	2	5
HOARSENESS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	8 / 259 (3.09%)
occurrences (all)	3	8
HYPOXIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
LARYNGEAL HEMORRHAGE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	2
LARYNGEAL MUCOSITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1

LUNG INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
NASAL CONGESTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ORTHOPNEA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PAIN LARYNX		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PHARYNGEAL MUCOSITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PHARYNGOLARYNGEAL PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PLEURAL EFFUSION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	6 / 255 (2.35%)	11 / 259 (4.25%)
occurrences (all)	6	14
PLEURITIC PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1
PNEUMONITIS		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	3 / 255 (1.18%)	4 / 259 (1.54%)
occurrences (all)	3	5
PNEUMOTHORAX		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	5 / 255 (1.96%)	1 / 259 (0.39%)
occurrences (all)	5	1
POSTNASAL DRIP		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)
occurrences (all)	2	0
PRODUCTIVE COUGH		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	8 / 259 (3.09%)
occurrences (all)	4	10
PULMONARY EDEMA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
PULMONARY FIBROSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RESPIRATORY FAILURE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	7 / 259 (2.70%)
occurrences (all)	3	8
RHINITIS SICCA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
RIGHT BASAL HYPOVENTILATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0

RIGHT PULMONARY HYPOVENTILATION		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
RUNNING NOSE		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
SINUS DISORDER		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
SNEEZING		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
SORE THROAT		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	4 / 259 (1.54%)
occurrences (all)	2	4
STRIDOR		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
VOICE ALTERATION		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)
occurrences (all)	2	0
WHEEZE		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	2
WHEEZING		
alternative dictionary used: NCI- CTCAE 4.0		

subjects affected / exposed	2 / 255 (0.78%)	4 / 259 (1.54%)	
occurrences (all)	2	5	
Psychiatric disorders			
AGITATION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences (all)	0	2	
ANXIETY			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	9 / 255 (3.53%)	8 / 259 (3.09%)	
occurrences (all)	13	10	
CONFUSION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	4 / 255 (1.57%)	8 / 259 (3.09%)	
occurrences (all)	4	9	
DELIRIUM			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
DEPRESSION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	5 / 255 (1.96%)	7 / 259 (2.70%)	
occurrences (all)	7	8	
HALLUCINATIONS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences (all)	2	0	
INSOMNIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	12 / 255 (4.71%)	12 / 259 (4.63%)	
occurrences (all)	15	14	
PSYCHIATRIC DISORDER OTHER: ADAPTIVE DISORDER			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
RESTLESSNESS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
SUICIDE ATTEMPT			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences (all)	1	1	
Investigations			
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	3 / 255 (1.18%)	0 / 259 (0.00%)	
occurrences (all)	5	0	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	4 / 255 (1.57%)	4 / 259 (1.54%)	
occurrences (all)	4	4	
C REACTIVE PROTEIN			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
CARBON MONOXIDE DIFFUSING CAPACITY DECREASED			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
C-REACTIVE PROTEIN INCREASED			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	2 / 255 (0.78%)	2 / 259 (0.77%)	
occurrences (all)	2	2	
CREATININE INCREASED			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
ELEVATED C REACTIVE PROTEIN VALUES		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
EOSINOPHIL COUNT INCREASED		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
GGT INCREASED		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	7 / 255 (2.75%)	3 / 259 (1.16%)
occurrences (all)	9	6
HYPOMAGNESEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
IRON DEFICIENCY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
LDH INCREASED		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
LEUCOCYTES AND C REACTIVE PROTEIN INCREASED		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
LOSS OF WEIGHT		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
LOW VITAMIN D		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
LYMPHOCYTE COUNT DECREASED		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	3
NEUTROPHIL COUNT DECREASED		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PLATELET COUNT DECREASED		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RAISED CRP		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
URAEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
WEIGHT LOSS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
WEIGHT GAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	34 / 255 (13.33%)	50 / 259 (19.31%)
occurrences (all)	56	97

WEIGHT LOSS alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	71 / 255 (27.84%) 97	95 / 259 (36.68%) 172	
Injury, poisoning and procedural complications			
ANKLE FRACTURE alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
ARTIPHICIAL SPHINTER RUPTURE alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
DERMATITIS RADIATION alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 255 (0.39%) 1	0 / 259 (0.00%) 0	
FALL alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	3 / 255 (1.18%) 3	3 / 259 (1.16%) 3	
FRACTURE alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	4 / 255 (1.57%) 5	2 / 259 (0.77%) 2	
HIP DISLOCATION alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 255 (0.39%) 3	0 / 259 (0.00%) 0	
OCCLUSION OF STENT alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
POSTTHORACOTOMY SYNDROM alternative dictionary used: NCI-			

CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	2	0	
WOUND COMPLICATION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
WOUND HAND			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences (all)	2	0	
ASYSTOLE			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
ATRIAL FIBRILLATION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	4 / 255 (1.57%)	6 / 259 (2.32%)	
occurrences (all)	4	7	
ATRIAL FLUTTER			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	3 / 259 (1.16%)	
occurrences (all)	0	4	
CARDIAC ARREST			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
CARDIAC TOXICITY			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
CARDIOGENIC SHOCK		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
CHEST PAIN - CARDIAC		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
CIRCULATORY INSUFFICIENCY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
CORONARY INSUFFICIENCY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
EXTRASYSTOLEN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HEART FAILURE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	3
MOBITZ (TYPE) II ATRIOVENTRICULAR BLOCK		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
MYOCARDIAL INFARCTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1

PALPITATIONS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PERICARDIAL EFFUSION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
PERICARDIAL TAMPONADE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PERICARDITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
RIGHT VENTRICULAR DYSFUNCTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SINUS BRADYCARDIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
SINUS TACHYCARDIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	3 / 259 (1.16%)
occurrences (all)	3	3
SUPRAVENTRICULAR EXTRASYSTOLE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
TACHYCARDIA		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences (all)	1	1	
VALVULAR HEART DEFECT			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
AKATHISIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)	
occurrences (all)	1	1	
AMNESIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
APHONIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	3 / 255 (1.18%)	1 / 259 (0.39%)	
occurrences (all)	3	1	
ATAXIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	6 / 259 (2.32%)	
occurrences (all)	0	7	
CEREBROSPINAL FLUID FISTULA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
COGNITIVE DISTURBANCE			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
CONCENTRATION IMPAIRMENT			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
DIZZINESS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	12 / 255 (4.71%)	10 / 259 (3.86%)
occurrences (all)	12	11
DYSIDIADOCHOKINESIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
DYSESTHESIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1
DYSGEUSIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	27 / 255 (10.59%)	23 / 259 (8.88%)
occurrences (all)	28	41
DYSPHASIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
EXTRAPYRAMIDAL DISORDER		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
FACIAL NERVE DISORDER		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
HEADACHE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	15 / 255 (5.88%)	19 / 259 (7.34%)
occurrences (all)	19	20

INTRACRANIAL HEMORRHAGE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)
occurrences (all)	0	3
LETHARGY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	6
MOVEMENTS INVOLUNTARY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
NEURALGIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)
occurrences (all)	0	2
NUMBNESS ON THE TIP OF FINGERS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
OCULOMOTOR NERVE DISORDER		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PARESTHESIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	9 / 255 (3.53%)	9 / 259 (3.47%)
occurrences (all)	10	9
PERIPHERAL MOTOR NEUROPATHY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	3 / 259 (1.16%)
occurrences (all)	5	7
PERIPHERAL SENSORY NEUROPATHY		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	11 / 255 (4.31%)	14 / 259 (5.41%)
occurrences (all)	11	18
POLYNEUROPATHY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PRESYNCOPE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)
occurrences (all)	2	0
RIGHT SIDED SCIATICA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SEIZURE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	3
SOMNOLENCE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	3 / 259 (1.16%)
occurrences (all)	0	3
STROKE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	3 / 259 (1.16%)
occurrences (all)	1	6
SYNCOPE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	5 / 255 (1.96%)	4 / 259 (1.54%)
occurrences (all)	5	5
TRANSIENT ISCHEMIC ATTACKS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1

<p>TREMOR</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 255 (0.78%)</p> <p>2</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>Blood and lymphatic system disorders</p> <p>ANEMIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>FEBRILE NEUTROPENIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>NEUTROPENIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p> <p>3 / 255 (1.18%)</p> <p>3</p> <p>1 / 255 (0.39%)</p> <p>1</p>	<p>1 / 259 (0.39%)</p> <p>1</p> <p>13 / 259 (5.02%)</p> <p>17</p> <p>0 / 259 (0.00%)</p> <p>0</p>	
<p>Ear and labyrinth disorders</p> <p>DISORDERS OF EQUILIBRUM</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>EAR PAIN</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>EXTERNAL EAR INFLAMMATION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>HEARING IMPAIRED</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>TINNITUS</p>	<p>1 / 255 (0.39%)</p> <p>1</p> <p>0 / 255 (0.00%)</p> <p>0</p> <p>0 / 255 (0.00%)</p> <p>0</p> <p>6 / 255 (2.35%)</p> <p>6</p>	<p>0 / 259 (0.00%)</p> <p>0</p> <p>1 / 259 (0.39%)</p> <p>1</p> <p>1 / 259 (0.39%)</p> <p>1</p> <p>3 / 259 (1.16%)</p> <p>3</p>	

<p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 255 (2.35%)</p> <p>9</p>	<p>3 / 259 (1.16%)</p> <p>5</p>	
<p>VERTIGO</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 255 (3.14%)</p> <p>9</p>	<p>13 / 259 (5.02%)</p> <p>20</p>	
<p>VESTIBULAR DISORDER</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>Eye disorders</p> <p>BAD VISION RIGHT EYE</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BLURRED VISION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CONJUNCTIVITIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CONJUNCTIVITIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DRY EYE</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>EXTRAOCULAR MUSCLE PARESIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p>	<p>1 / 255 (0.39%)</p> <p>1</p> <p>3 / 255 (1.18%)</p> <p>3</p> <p>1 / 255 (0.39%)</p> <p>1</p> <p>7 / 255 (2.75%)</p> <p>8</p> <p>4 / 255 (1.57%)</p> <p>4</p>	<p>0 / 259 (0.00%)</p> <p>0</p> <p>6 / 259 (2.32%)</p> <p>6</p> <p>0 / 259 (0.00%)</p> <p>0</p> <p>6 / 259 (2.32%)</p> <p>9</p> <p>6 / 259 (2.32%)</p> <p>6</p>	

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
EYE DISORDER OTHER- HEMORRHAGE EYE		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
EYE IRRITATION		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
EYE PAIN		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	3 / 259 (1.16%)
occurrences (all)	2	3
INFLAMMATION RIGHT EYE		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
INTENSIFIED TEAR FLUID		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
OSCILLOPSIA		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PAPILLEDEMA		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
REDUCED VISION		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1

<p>SUB CONJUNCTIVAL HEMORRHAGE (LEFT EYE)</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>0 / 259 (0.00%)</p> <p>0</p>	
<p>SUBCONJUNCTIVAL HEMORRHAGE RIGHT EYE</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>VISUAL DISTURBANCES</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>0 / 259 (0.00%)</p> <p>0</p>	
<p>WATERING EYES</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 255 (3.14%)</p> <p>11</p>	<p>7 / 259 (2.70%)</p> <p>10</p>	
<p>Gastrointestinal disorders</p> <p>ABDOMINAL DISTENSION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ABDOMINAL PAIN</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ANAL ABSCESS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ANAL FISTULA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ANAL HEMORRHAGE</p>	<p>2 / 255 (0.78%)</p> <p>2</p> <p>14 / 255 (5.49%)</p> <p>16</p> <p>0 / 255 (0.00%)</p> <p>0</p> <p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>1</p> <p>21 / 259 (8.11%)</p> <p>35</p> <p>1 / 259 (0.39%)</p> <p>1</p> <p>2 / 259 (0.77%)</p> <p>2</p>	

alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
ANAL MUCOSITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ANAL PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ASCITES		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
BLEEDING SPLEEN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
BLOATING		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	2
CHEILITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
COLITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	3 / 259 (1.16%)
occurrences (all)	3	3
COLONDIVERTICULOSIS		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
COLONIC OBSTRUCTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
CONSTIPATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	54 / 255 (21.18%)	69 / 259 (26.64%)
occurrences (all)	71	94
CONTIPATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DENTAL CARIES		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DIARRHEA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	41 / 255 (16.08%)	53 / 259 (20.46%)
occurrences (all)	57	74
DIGESTION PROBLEMS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DIVERTICULITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DIVERTICULOSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1

<p>DRY MOUTH</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>5 / 259 (1.93%)</p> <p>5</p>	
<p>DYSGEUSIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>2</p>	<p>0 / 259 (0.00%)</p> <p>0</p>	
<p>DYSPEPSIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 255 (2.75%)</p> <p>10</p>	<p>7 / 259 (2.70%)</p> <p>8</p>	
<p>DYSPHAGIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>9 / 255 (3.53%)</p> <p>12</p>	<p>9 / 259 (3.47%)</p> <p>10</p>	
<p>ENTEROCOLITIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>2 / 259 (0.77%)</p> <p>4</p>	
<p>EPIGASTRIC DISCOMFORT</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>ESOPHAGEAL FISTULA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>ESOPHAGEAL OBSTRUCTION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>0 / 259 (0.00%)</p> <p>0</p>	
<p>ESOPHAGEAL PAIN</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p>			

subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
ESOPHAGEAL STENOSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
ESOPHAGITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	2 / 259 (0.77%)
occurrences (all)	6	2
FATIGUE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
FLATULENCE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
GASTRIC ULCER		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
GASTRITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	3 / 259 (1.16%)
occurrences (all)	3	4
GASTROESOPHAGEAL REFLUX DISEASE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	9 / 259 (3.47%)
occurrences (all)	4	10
GASTROINTESTINAL BLEEDING		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0

GASTROINTESTINAL DISORDERS - OTHER:UMBILICAL HERNIA		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
GASTROINTESTINAL PAIN		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
GINGIVAL PAIN		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HEMORRHOIDAL HEMORRHAGE		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
HEMORRHOIDS		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	4 / 259 (1.54%)
occurrences (all)	5	4
ILEUS		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)
occurrences (all)	2	0
MUCOSITIS ORAL		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	34 / 255 (13.33%)	42 / 259 (16.22%)
occurrences (all)	38	62
NAUSEA		
alternative dictionary used: NCI- CTCAE 4.0		
subjects affected / exposed	91 / 255 (35.69%)	92 / 259 (35.52%)
occurrences (all)	147	162
NEUTROPENIC ENTEROCOLITIS		
alternative dictionary used: NCI- CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ODYNOPHAGIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ORAL PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	4 / 259 (1.54%)
occurrences (all)	1	4
PERIODONTAL DISEASE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	4 / 259 (1.54%)
occurrences (all)	0	4
PERIOTONDAL DISEASE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RECTAL HEMORRHAGE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	0 / 259 (0.00%)
occurrences (all)	3	0
RECTAL MUCOSITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SIGMADIVERTICULITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SORE, SWOLLEN TONGUE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1

<p>STOMACH PAIN</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 255 (3.92%)</p> <p>10</p>	<p>2 / 259 (0.77%)</p> <p>2</p>	
<p>TOOTH EXTRACTION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>TOOTHACHE</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>2 / 259 (0.77%)</p> <p>2</p>	
<p>UPPER GASTROINTESTINAL HEMORRHAGE</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>2</p>	
<p>VOMITING</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>45 / 255 (17.65%)</p> <p>61</p>	<p>45 / 259 (17.37%)</p> <p>67</p>	
<p>VOMITTING</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 255 (0.78%)</p> <p>2</p>	<p>0 / 259 (0.00%)</p> <p>0</p>	
<p>Hepatobiliary disorders</p> <p>BILE DUCT STENOSIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>0 / 259 (0.00%)</p> <p>0</p>	
<p>CHOLANGITIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 255 (0.39%)</p> <p>1</p>	<p>0 / 259 (0.00%)</p> <p>0</p>	
<p>CHOLECYSTITIS</p> <p>alternative dictionary used: NCI-</p>			

CTCAE 4.0			
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)	
occurrences (all)	3	0	
HEPATIC PAIN			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
LIVER CONGESTION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
LIVER LIPOMAS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
TRANSAMINITIS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
WORSENING LIVER FUNCTION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
ACTINITIC KERATOSIS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
ALOPECIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	6 / 255 (2.35%)	9 / 259 (3.47%)	
occurrences (all)	6	10	
BULLOUS DERMATITIS			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
CELLULITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DARK SKIN DISCOLORATION AXILLAR, SHOULDER		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
DRY SKIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	7 / 259 (2.70%)
occurrences (all)	4	7
ECZEMA ARMS AND ABDOMINAL		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ERYSIPELAS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	2
ERYTHEMA MULTIFORME		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	8 / 259 (3.09%)
occurrences (all)	4	8
EXANTHEMA BOTH ARMS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
FACIAL WOUND		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0

FRAGILITY ON NAILS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
HAIR WEAKNESS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HYPERHIDROSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	4 / 259 (1.54%)
occurrences (all)	4	6
NAIL DISCOLORATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
NAIL RIDGING		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PERIANAL IRRITATION, WARTS BACK / ONE WART RIGHT EYE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PERIORBITAL EDEMA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)
occurrences (all)	0	2
PRURITUS		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	7 / 255 (2.75%)	7 / 259 (2.70%)
occurrences (all)	12	7
PSORIASIS REACTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RASH		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
RASH ACNEIFORM		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	6 / 255 (2.35%)	10 / 259 (3.86%)
occurrences (all)	6	10
RASH MACULO-PAPULAR		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	8 / 255 (3.14%)	14 / 259 (5.41%)
occurrences (all)	10	17
RASH ON ARMS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SKIN HYPERPIGMENTATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SKIN ULCERATION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	3 / 259 (1.16%)
occurrences (all)	5	3
TICK BITE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0

<p>TOXIC EPIDERMAL NECROLYSIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 255 (0.00%)</p> <p>0</p>	<p>1 / 259 (0.39%)</p> <p>1</p>	
<p>URTICARIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 255 (1.18%)</p> <p>3</p>	<p>3 / 259 (1.16%)</p> <p>4</p>	
<p>Renal and urinary disorders</p> <p>ACUTE KIDNEY INJURY</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CHRONIC KIDNEY DISEASE</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CYSTITIS</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CYSTITIS NONINFECTIVE</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSURIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>HEMATURIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>NYCTURIA</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p>	<p>8 / 255 (3.14%)</p> <p>11</p> <p>2 / 255 (0.78%)</p> <p>2</p> <p>0 / 255 (0.00%)</p> <p>0</p> <p>1 / 255 (0.39%)</p> <p>1</p> <p>1 / 255 (0.39%)</p> <p>1</p> <p>1 / 255 (0.39%)</p> <p>2</p>	<p>4 / 259 (1.54%)</p> <p>5</p> <p>3 / 259 (1.16%)</p> <p>4</p> <p>1 / 259 (0.39%)</p> <p>1</p> <p>0 / 259 (0.00%)</p> <p>0</p> <p>2 / 259 (0.77%)</p> <p>2</p>	

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PROTEINURIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RENAL AND URINARY DISORDERS - RENAL PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
RENAL COLIC		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RENAL FAILURE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
RENAL INSUFFICIENCY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	3	1
URINARY FREQUENCY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)
occurrences (all)	0	2
URINARY INCONTINENCE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	1	2
URINARY RETENTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1

<p>URINARY TRACT INFECTION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>URINARY TRACT OBSTRUCTION</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>URINARY TRACT PAIN</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>URINARY URGENCY</p> <p>alternative dictionary used: NCI-CTCAE 4.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>			
	1 / 255 (0.39%)	0 / 259 (0.00%)	
	1	0	
	2 / 255 (0.78%)	0 / 259 (0.00%)	
	3	0	
	3 / 255 (1.18%)	1 / 259 (0.39%)	
	3	1	
	1 / 255 (0.39%)	0 / 259 (0.00%)	
	1	0	
Endocrine disorders			
ADRENAL INSUFFICIENCY			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
CUSHINGOID			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
HYPERTHYROIDISM			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
HYPOTHYROIDISM			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	3 / 259 (1.16%)	
occurrences (all)	0	3	
THYROIDITIS			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	6 / 255 (2.35%)	11 / 259 (4.25%)	
occurrences (all)	6	13	
ARTHRITIS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)	
occurrences (all)	1	2	
BACK PAIN			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	22 / 255 (8.63%)	24 / 259 (9.27%)	
occurrences (all)	33	33	
BONE PAIN			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	18 / 255 (7.06%)	12 / 259 (4.63%)	
occurrences (all)	21	18	
CHEST WALL PAIN			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	6 / 255 (2.35%)	6 / 259 (2.32%)	
occurrences (all)	6	10	
FLANK PAIN			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	3 / 255 (1.18%)	5 / 259 (1.93%)	
occurrences (all)	4	5	
GENERALIZED MUSCLE WEAKNESS			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	2 / 255 (0.78%)	2 / 259 (0.77%)	
occurrences (all)	2	2	
HERNIATED DISC			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
JOINT EFFUSION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)
occurrences (all)	0	2
LEFT SHOULDER PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
MUSCLE WEAKNESS LOWER LIMB		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	4 / 259 (1.54%)
occurrences (all)	1	5
MUSCLE WEAKNESS UPPER LIMB		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)
occurrences (all)	2	0
MUSCULOSKELETAL PAIN		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
MUSCULOSKELETAL PAIN - RIGHT HIP		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
MYALGIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	5 / 259 (1.93%)
occurrences (all)	3	6
MYOSITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1

NECK PAIN alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	3 / 255 (1.18%) 3	4 / 259 (1.54%) 4	
OSTEONECROSIS OF JAW alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	3 / 259 (1.16%) 3	
PAIN IN EXTREMITY alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	12 / 255 (4.71%) 14	14 / 259 (5.41%) 16	
PAIN LEFT AXILLA alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 255 (0.39%) 1	0 / 259 (0.00%) 0	
PAIN OTHER - RIGHT GLUTEAL AREA alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 255 (0.39%) 1	0 / 259 (0.00%) 0	
PAIN RIGHT MANDIBULA alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 255 (0.39%) 1	0 / 259 (0.00%) 0	
SHOULDER PAIN alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
TENDONITIS alternative dictionary used: NCI-CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 255 (0.00%) 0	1 / 259 (0.39%) 1	
Infections and infestations			

APPENDICITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
BLADDER INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
BRONCHIAL INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	9 / 255 (3.53%)	11 / 259 (4.25%)
occurrences (all)	12	14
CATHETER RELATED INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
ENTEROBACTER CLOACAO INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
ENTEROCOLITIS INFECTIOUS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
ESOPHAGEAL INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
FLU LIKE SYMPTOMS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HERPES ZOSTER		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	3 / 259 (1.16%)
occurrences (all)	0	3
INFECTION OF UNCLEAR GENESIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
INFECTIONS & INFESTATIONS		
OTHER - HEAD COLD		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
INFLUENZA A		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
INFLUENZA B		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
JOINT INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
KIDNEY INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
LARYNGITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0

LIP INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	4 / 255 (1.57%)	1 / 259 (0.39%)
occurrences (all)	4	1
LOWER RESPIRATORY TRACT INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
LUNG INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	24 / 255 (9.41%)	40 / 259 (15.44%)
occurrences (all)	34	55
MENINGITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
MUCOSAL INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	4 / 259 (1.54%)
occurrences (all)	1	5
MYCOSIS (IN OESOPHAGUS)		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ORAL VIRAL EVENT		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PAPULOPUSTULAR RASH		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PAROTIDITIS		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
PENILE INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
PERSISTING INFLAMMATION DUE TO MALIGNANCY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PHARYNGITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	3 / 259 (1.16%)
occurrences (all)	2	3
PHLEBITIS INFECTIVE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
PLEURAL INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1
RASH PUSTULAR		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	3 / 259 (1.16%)
occurrences (all)	1	3
RESPIRATORY INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
RESPIRATORY TRACT INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1

RHINITIS INFECTIVE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	2 / 259 (0.77%)
occurrences (all)	3	2
SCROTAL INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SEPSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	10 / 255 (3.92%)	11 / 259 (4.25%)
occurrences (all)	15	16
SEPTIC SHOCK		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SINUSITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	1 / 259 (0.39%)
occurrences (all)	2	1
SKIN INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	3 / 255 (1.18%)	7 / 259 (2.70%)
occurrences (all)	4	9
STOMA SITE INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
STOMATITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SUSPECTED INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
SUSPECTED INFECTION OF RICKHAM RESERVOIR		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
TOOTH INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	2
TRACHEITIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1
UNCLEAR INFECT-FOCUS, NO GERM-EVIDENCE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
UPPER RESPIRATORY INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	18 / 255 (7.06%)	24 / 259 (9.27%)
occurrences (all)	22	33
UPPER RESPIRATORY TRACT INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
URETHRAL INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)
occurrences (all)	0	2
URINARY TRACT INFECTION		
alternative dictionary used: NCI-CTCAE 4.0		

subjects affected / exposed	9 / 255 (3.53%)	11 / 259 (4.25%)	
occurrences (all)	9	12	
VIRAL INFECTION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
VULVAL INFECTION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
WOUND INFECTION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	2 / 259 (0.77%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
ANOREXIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	61 / 255 (23.92%)	68 / 259 (26.25%)	
occurrences (all)	84	104	
APPETITE INCREASED			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	1	0	
CACHEXIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
DEHYDRATION			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	3 / 255 (1.18%)	9 / 259 (3.47%)	
occurrences (all)	4	11	
DIABETIC KETOSIS WITH METABOLIC ALKALOSIS			
alternative dictionary used: NCI-CTCAE 4.0			

subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
ELECTROLYTE DEFICIENCY		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
EXSICCOSIS		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
GLUCOSE INTOLERANCE		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)
occurrences (all)	1	0
HYPERCHOLESTEROLEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)
occurrences (all)	0	1
HYPERGLYCEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	5 / 255 (1.96%)	5 / 259 (1.93%)
occurrences (all)	6	19
HYPERKALEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	2 / 259 (0.77%)
occurrences (all)	2	3
HYPERURICEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	2 / 255 (0.78%)	0 / 259 (0.00%)
occurrences (all)	2	0
HYPOGLYCEMIA		
alternative dictionary used: NCI-CTCAE 4.0		
subjects affected / exposed	1 / 255 (0.39%)	1 / 259 (0.39%)
occurrences (all)	1	1

HYPOKALEMIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	7 / 255 (2.75%)	11 / 259 (4.25%)	
occurrences (all)	9	15	
HYPOMAGNESEMIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	9 / 255 (3.53%)	7 / 259 (2.70%)	
occurrences (all)	23	11	
HYPONATREMIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	8 / 255 (3.14%)	9 / 259 (3.47%)	
occurrences (all)	9	15	
HYPOPHOSPHATEMIA			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	3 / 255 (1.18%)	10 / 259 (3.86%)	
occurrences (all)	3	19	
LOSS OF APPETITE			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	0 / 255 (0.00%)	1 / 259 (0.39%)	
occurrences (all)	0	1	
PSEUDOGOUT			
alternative dictionary used: NCI-CTCAE 4.0			
subjects affected / exposed	1 / 255 (0.39%)	0 / 259 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2016	This is a scientific amendment and major changes included: Trial treatment was amended to encompass first-line platinum-based doublet chemotherapy in arm A, First-line platinum-based doublet chemotherapy and lifelong denosumab in B. For the exclusion criteria of Patients with presence of documented sensitizing EGFR activating mutation or ALK rearrangements, EGFR and ALK testing was not mandatory but recommended to be done. If test had been ordered, investigator was encouraged to wait for the result before enrolment. Once the patient was enrolled, if an EGFR mutation/ALK alteration was confirmed, no EGFR or ALK TKi treatment respectively was to be started until PD to first-line platinum-based chemotherapy. The use Prior chemotherapy or molecular targeted therapy for metastatic disease was an exclusion criteria in the previous version and this was extended to include the following exceptions for safety concerns: Neoadjuvant or adjuvant chemotherapy or radio-chemotherapy are allowed if terminated more than 6 months before registration. Previous radical radiotherapy without systemic treatment is allowed. One previous line of systemic immunotherapy by checkpoint inhibitors is allowed. Concomitant treatment with immune checkpoint inhibitors. The inclusion criteria of measurable or evaluable disease (according to RECIST 1.1 criteria) was extended to include assessment within 28 days from randomization. For statistical considerations, recent introduction of anti PD-1/PD-L1 immunotherapy may change the expectation of overall survival in the patient population. Nevertheless, the current trial hypothesis on the primary endpoint OS relies on the relative change (Hazard Ratio). Therefore, the increase in OS in the targeted population will not affect the sample size but will increase the follow up time needed to reach the number of events required for the final analysis by about 5 months.
20 January 2017	The protocol was updated to add clarifications and to eliminate ambiguities. In addition, the prior use of immune checkpoint inhibitors as well as the addition of bevacizumab to chemotherapy is now allowed, based on the recent introduction of these treatments in the therapy of lung cancer. Furthermore the AE reporting after first line platinum-based doublet chemotherapy has been simplified. Recent introduction of anti PD-1/PD-L1 immunotherapy may change the expectation of overall survival in the patient population, given the anticipated effect of such immunotherapy on survival and the changes made to the inclusion criteria, the Statistical chapter has been updated and primary analysis to compare the experimental versus the control arms for the time to event endpoints will be based on Cox regression adjusted for the stratification factors, receiving prior anti PD-1/PD-L1 immunotherapy administration (Yes vs No) and an indicator whether the patient was included in the pre- or post-amendment protocol (Yes vs No).prior anti PD-L1 therapy or not in addition to the stratification factors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study steering committee decided to close the study prematurely due to poor accrual. The primary analysis is therefore underpowered

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32565388>