Clinical trial results:
An Open Label, Multicenter Extension Study to Evaluate the Safety of R935788 in Patients with Rheumatoid Arthritis Who Have Completed the Treatment Phase of a Rigel-Sponsored R935788 Study

Summary

EudraCT number	2008-000744-13
Trial protocol	DE BE FR IT BG
Global end of trial date	21 August 2013

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	C-935788-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00805467
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Pharmaceuticals
Sponsor organisation address	Alderley Park, Macclesfield, United Kingdom,
Public contact	Neil Mackillop, AstraZeneca, information.center@astrazeneca.com
Scientific contact	Neil Mackillop, AstraZeneca, neil.mackillop@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 August 2013
Global end of trial reached?	Yes
Global end of trial date	21 August 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to investigate the long-term safety of fostamatinib in patients with RA who completed the treatment phase of Study C-788-006X, C-788-010, or C-788-011.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practices (GCPs) and applicable laws and regulations.
Patients provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment prior to admission to this study.
The study was approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) before the start of the study.

Background therapy:

Patients may receive stable doses of methotrexate (with folic or folinic acid), azathioprine (not in combination with methotrexate), leflunomide (not in combination with methotrexate), sulfasalazine, chloroquine, hydroxychloroquine, gold, NSAIDs (including COX2 inhibitors), minocycline, or doxycycline.

Evidence for comparator: -

Actual start date of recruitment	29 August 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Colombia: 146
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Mexico: 127
Country: Number of subjects enrolled	Peru: 7
Country: Number of subjects enrolled	Poland: 61
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	United States: 226

Worldwide total number of subjects	624
EEA total number of subjects	118

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)	513
From 65 to 84 years	110
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 624 patients were enrolled: 1, 59, 183 & 381 were allocated to the 50mg twice daily (bid), 100 mg once daily (qd), 150 mg qd and 100 mg bid groups, respectively. As this was a long-term extension study no specific end date was given. Patients who were ongoing when the study was terminated are shown as completers.

Pre-assignment

Screening details:

Treatments were assigned according to those given in the qualifying studies. All patients received investigational product.

Period 1

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

Blinding implementation details:

This an open label extension study, but patients will remain blinded to their treatment assignment from the previous feeder study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fostamatinib 50 mg bid

Arm description:

Oral treatment

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

Dosage and administration details:

50mg twice daily

Arm title	Fostamatinib 100 mg qd

Arm description:

Oral treatment

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

Dosage and administration details:

100mg once daily

Arm title	Fostamatinib 150 mg qd

Arm description:

Oral treatment

Arm type	Experimental

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

Dosage and administration details:
150mg once daily

Arm title	Fostamatinib 100 mg bid

Arm description:
Oral treatment

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

Dosage and administration details:
100mg twice daily

Number of subjects in period 1	Fostamatinib 50 mg bid	Fostamatinib 100 mg qd	Fostamatinib 150 mg qd
Started	1	59	183
Completed	1	25	80
Not completed	0	34	103
Adverse event, serious fatal	-	2	7
Consent withdrawn by subject	-	6	45
Physician decision	-	1	2
Adverse event, non-fatal	-	13	26
Not reported	-	-	3
Lost to follow-up	-	1	7
Lack of efficacy	-	8	13
Protocol deviation	-	3	-

Number of subjects in period 1	Fostamatinib 100 mg bid
Started	381
Completed	144
Not completed	237
Adverse event, serious fatal	5
Consent withdrawn by subject	50
Physician decision	6
Adverse event, non-fatal	57
Not reported	7
Lost to follow-up	21

Lack of efficacy	86
Protocol deviation	5

Baseline characteristics

Reporting groups	
Reporting group title	Fostamatinib 50 mg bid
Reporting group description:	
Oral treatment	
Reporting group title	Fostamatinib 100 mg qd
Reporting group description:	
Oral treatment	
Reporting group title	Fostamatinib 150 mg qd
Reporting group description:	
Oral treatment	
Reporting group title	Fostamatinib 100 mg bid
Reporting group description:	
Oral treatment	

Reporting group values	Fostamatinib 50 mg bid	Fostamatinib 100 mg qd	Fostamatinib 150 mg qd
Number of subjects	1	59	183
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	52	151
From 65-84 years	1	7	32
85 years and over	0	0	0
Age Continuous |			
Units: years			
arithmetic mean	70	51.4	51.7
standard deviation	± 0	± 11.15	± 13.32
Gender, Male/Female			
Units: Participants			
Female	1	53	157
Male	0	6	26
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	0	18	88
Black	1	1	6
Hispanic	0	40	88
Asian	0	0	0
Other	0	0	1

Reporting group values	Fostamatinib 100 mg bid	Total	
Number of subjects	381	624	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	310	513	
From 65-84 years	70	110	
85 years and over	1	1	
Age Continuous | Units: years			
arithmetic mean	53.8		
standard deviation	± 12.36	-	
Gender, Male/Female Units: Participants			
Female	324	535	
Male	57	89	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	184	290	
Black	14	22	
Hispanic	179	307	
Asian	2	2	
Other	2	3	

End points

End points reporting groups

Reporting group title	Fostamatinib 50 mg bid
Reporting group description: Oral treatment	
Reporting group title	Fostamatinib 100 mg qd
Reporting group description: Oral treatment	
Reporting group title	Fostamatinib 150 mg qd
Reporting group description: Oral treatment	
Reporting group title	Fostamatinib 100 mg bid
Reporting group description: Oral treatment	

Primary: Percentage of patients who had at least 1 treatment emergent adverse event in any category

End point title	Percentage of patients who had at least 1 treatment emergent adverse event in any category[1]
End point description: AE = adverse event, bid = twice daily, IP = investigational product, qd = once daily, SAE = serious adverse event	
End point type	Primary
End point timeframe: Entry in extension to end of study, up to a maximum of 5 years. (Variable by subject - median duration of 3 years)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data not avaliable as it is observational study.

End point values	Fostamatinib 50 mg bid	Fostamatinib 100 mg qd	Fostamatinib 150 mg qd	Fostamatinib 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	59	183	381
Units: % of patients				
number (not applicable)				
Any AE	100	91.5	90.7	88.7
Any fatal AE	0	1.7	3.8	1.6
Any SAE (including fatal AEs)	100	3.4	18.6	20.2
Any AE leading to termination of study therapy	0	22	16.4	15.2

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28-CRP score

End point title	DAS28-CRP score

End point description:

The Disease Activity Score 28 using C-Reactive Protein (DAS28-CRP) is a measure of disease activity in rheumatoid arthritis (RA) and assesses the 28 joints RA commonly affects; the score includes the number of tender and swollen joints (out of 28), CRP level (a measure of inflammation in the blood), and the patient's global assessment of health (ranging from very good to very bad). These measures are then fed into a complex mathematical formula to produce the overall DAS on a scale from 1 to 10, where scores greater than 5.1 are considered to indicate active disease, scores less than 3.2 are considered to indicate with well controlled disease, and scores less than 2.6 are considered to indicate remission. bid = twice daily, CRP = C-reactive protein, DAS28 = Disease Activity Score based on a 28 joint count, n/a = not applicable, qd = once daily

End point type	Secondary

End point timeframe:

3 years

End point values	Fostamatinib 50 mg bid	Fostamatinib 100 mg qd	Fostamatinib 150 mg qd	Fostamatinib 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[2]	55	181	374
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline (n=1, 55, 181, 374)	5.27 (± 0)	5.34 (± 1.123)	5.31 (± 1.162)	5.36 (± 1.259)
Quarter 4 (n=1, 41, 136, 254)	2 (± 0)	3.57 (± 1.408)	3.46 (± 1.282)	3.44 (± 1.453)
Quarter 8 (n=1, 33, 114, 201)	2.92 (± 0)	3.43 (± 1.412)	3.25 (± 1.29)	3.35 (± 1.484)
Quarter 12 (n=1, 30, 94, 174)	2.31 (± 0)	3.36 (± 1.376)	3.07 (± 1.055)	3.27 (± 1.373)

Notes:

[2] - Standard deviation not applicable for a single patient. 0 entered.

Statistical analyses

No statistical analyses for this end point

Secondary: HAQ-DI score

End point title	HAQ-DI score

End point description:

Health Assessment Questionnaire - Disability Index, a measure of physical function. The HAQ-DI score is calculated by summing the category scores from 8 sub-categories (ie, scores for patient ability in dressing and grooming, rising, eating, walking, hygeine, reach, grip and common daily activities) and dividing by the number of categories completed. The HAQ-DI score takes values between 0 and 3, with a higher score indicating greater disability. A HAQ-DI response is a reduction from baseline in HAQ-DI greater than or equal to the minimally important difference (0.22). BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, OR = odds ratio, PO = orally, QD = once a day.

End point type	Secondary

End point timeframe:

3 years

End point values	Fostamatinib 50 mg bid	Fostamatinib 100 mg qd	Fostamatinib 150 mg qd	Fostamatinib 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[3]	56	181	376
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Baseline (n=1, 56, 181, 376)	1.25 (± 0)	1.5 (± 0.735)	1.46 (± 0.707)	1.46 (± 0.715)
Quarter 4 (n=1, 41, 138, 254)	0.57 (± 0)	1 (± 0.677)	1.07 (± 0.726)	0.99 (± 0.722)
Quarter 8 (n=1, 33, 107, 201)	0.43 (± 0)	1 (± 0.657)	1.02 (± 0.72)	0.95 (± 0.703)
Quarter 12 (n=1, 30, 94, 176)	0.38 (± 0)	1.01 (± 0.651)	0.98 (± 0.718)	0.96 (± 0.687)

Notes:

[3] - Standard deviation not applicable for a single patient. 0 entered.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: As this was an ongoing long term extension study the timeframe for adverse reporting is from the start of the study (August 2008) until study termination (August 2013).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	100 MG QD
Reporting group description: Fostamatinib 100mg once daily	
Reporting group title	100 MG BID
Reporting group description: Fostamatinib 100mg twice daily	
Reporting group title	50 MG BID
Reporting group description: Fostamatinib 50mg twice daily	
Reporting group title	150 MG QD
Reporting group description: Fostamatinib 150mg once daily	

Serious adverse events	100 MG QD	100 MG BID	50 MG BID
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 59 (3.39%)	77 / 381 (20.21%)	1 / 1 (100.00%)
number of deaths (all causes)	1	6	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANAL CANCER			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BASOSQUAMOUS CARCINOMA OF SKIN			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRAIN NEOPLASM MALIGNANT			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
BREAST CANCER			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLON CANCER STAGE IV			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CERVIX CARCINOMA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINE CARCINOMA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARATHYROID TUMOUR BENIGN			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG SQUAMOUS CELL CARCINOMA STAGE UNSPECIFIED			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE LEIOMYOMA			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THYROID CANCER			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
AORTIC ANEURYSM			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIOSCLEROSIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
HIP ARTHROPLASTY			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMPLANTABLE DEFIBRILLATOR			

INSERTION			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KNEE ARTHROPLASTY			
subjects affected / exposed	1 / 59 (1.69%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABORTION SPONTANEOUS INCOMPLETE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE DISLOCATION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			

subjects affected / exposed	1 / 59 (1.69%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
ENDOMETRIAL HYPERTROPHY			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN CYST			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTMENOPAUSAL HAEMORRHAGE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VAGINAL PROLAPSE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
ASTHMA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			

subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFILTRATION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY FIBROSIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
DISLOCATION OF VERTEBRA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCLE RUPTURE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

JOINT DISLOCATION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PUBIS FRACTURE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ARTERIOSPASM CORONARY			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			

subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIOPULMONARY FAILURE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTRACARDIAC THROMBUS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENTRICULAR DYSFUNCTION			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
ACUTE POLYNEUROPATHY			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL HAEMORRHAGE			

subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR RADICULOPATHY			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRESYNCOPE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADICULOPATHY			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOTIC THROMBOCYTOPENIC PURPURA			

subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
PANOPHTHALMITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 59 (0.00%)	3 / 381 (0.79%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
COLITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS MICROSCOPIC			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC POLYP			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULUM			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAECALOMA			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC PERFORATION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
GASTRITIS			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL PERFORATION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIATUS HERNIA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS HAEMORRHAGIC			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL PROLAPSE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UMBILICAL HERNIA			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLELITHIASIS			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC CIRRHOSIS			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC STEATOSIS			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
GOITRE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
CERVICAL SPINAL STENOSIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR SPINAL STENOSIS			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOSITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABSCESS SOFT TISSUE			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BURSITIS INFECTIVE			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	0 / 59 (0.00%)	4 / 381 (1.05%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS HEPATITIS			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSENTERY			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPIGLOTTITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYTHEMA MIGRANS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA SEPSIS			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GIARDIASIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTED BITES			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS BACTERIAL			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECROTISING FASCIITIS			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			

subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 59 (0.00%)	6 / 381 (1.57%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA STAPHYLOCOCCAL			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUSITIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			

subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VARICELLA			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION STAPHYLOCOCCAL			
subjects affected / exposed	0 / 59 (0.00%)	0 / 381 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 59 (0.00%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	0 / 59 (0.00%)	3 / 381 (0.79%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	150 MG QD		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 183 (18.58%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	3		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANAL CANCER			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BASOSQUAMOUS CARCINOMA OF SKIN			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRAIN NEOPLASM MALIGNANT			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BREAST CANCER			
subjects affected / exposed	2 / 183 (1.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
COLON CANCER STAGE IV			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CERVIX CARCINOMA			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LARGE INTESTINE CARCINOMA			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

PARATHYROID TUMOUR BENIGN				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LUNG SQUAMOUS CELL CARCINOMA STAGE UNSPECIFIED				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UTERINE LEIOMYOMA				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
THYROID CANCER				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
AORTIC ANEURYSM				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ARTERIOSCLEROSIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DEEP VEIN THROMBOSIS				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
HYPERTENSIVE CRISIS				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

HYPOTENSION				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
HIP ARTHROPLASTY				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
IMPLANTABLE DEFIBRILLATOR INSERTION				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
KNEE ARTHROPLASTY				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
ABORTION SPONTANEOUS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ABORTION SPONTANEOUS INCOMPLETE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
CHEST PAIN				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DEVICE DISLOCATION				

subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PYREXIA				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUDDEN DEATH				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
ENDOMETRIAL HYPERTROPHY				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OVARIAN CYST				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
POSTMENOPAUSAL HAEMORRHAGE				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VAGINAL PROLAPSE				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
ACUTE RESPIRATORY FAILURE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

ASTHMA				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LUNG INFILTRATION				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PULMONARY FIBROSIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
ANXIETY				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
DISLOCATION OF VERTEBRA				

subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MUSCLE RUPTURE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
JOINT DISLOCATION				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUBDURAL HAEMATOMA				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PUBIS FRACTURE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPINAL FRACTURE				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
ARTERIOSPASM CORONARY				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ATRIAL FIBRILLATION				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CARDIAC ARREST				

subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CARDIAC FAILURE				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
CARDIAC FAILURE CONGESTIVE				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CARDIO-RESPIRATORY ARREST				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
CARDIOPULMONARY FAILURE				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
CORONARY ARTERY DISEASE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTRACARDIAC THROMBUS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MYOCARDIAL INFARCTION				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VENTRICULAR DYSFUNCTION				

subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
ACUTE POLYNEUROPATHY			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LUMBAR RADICULOPATHY			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PRESYNCOPE			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RADICULOPATHY			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
SYNCOPE			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

ANAEMIA				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PANCYTOPENIA				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
THROMBOTIC THROMBOCYTOPENIC PURPURA				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Eye disorders				
PANOPHTHALMITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
ABDOMINAL PAIN				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COLITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COLITIS MICROSCOPIC				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COLONIC POLYP				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

DIARRHOEA			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DIVERTICULUM			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FAECALOMA			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTRIC PERFORATION			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTRITIS			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROINTESTINAL PERFORATION			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HIATUS HERNIA			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ILEUS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PANCREATITIS			

subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS ACUTE				
subjects affected / exposed	2 / 183 (1.09%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS HAEMORRHAGIC				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RECTAL PROLAPSE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
UMBILICAL HERNIA				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VOMITING				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
CHOLECYSTITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHOLECYSTITIS ACUTE				

subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CHOLELITHIASIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HEPATIC CIRRHOSIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HEPATIC STEATOSIS			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
GOITRE			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
CERVICAL SPINAL STENOSIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INTERVERTEBRAL DISC PROTRUSION			

subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MUSCULOSKELETAL PAIN				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LUMBAR SPINAL STENOSIS				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYOSITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RHEUMATOID ARTHRITIS				
subjects affected / exposed	2 / 183 (1.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
OSTEOARTHRITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPINAL OSTEOARTHRITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
ABSCESS SOFT TISSUE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
APPENDICITIS				

subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRONCHITIS				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BURSITIS INFECTIVE				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CELLULITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CYTOMEGALOVIRUS HEPATITIS				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CYTOMEGALOVIRUS INFECTION				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DIVERTICULITIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DYSENTERY				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
EPIGLOTTITIS				

subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ERYTHEMA MIGRANS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ESCHERICHIA SEPSIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
GIARDIASIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INFECTED BITES			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MENINGITIS BACTERIAL			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NECROTISING FASCIITIS			

subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
OSTEOMYELITIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PERITONITIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	3 / 183 (1.64%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA STAPHYLOCOCCAL			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PYELONEPHRITIS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SEPSIS			
subjects affected / exposed	2 / 183 (1.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
SEPTIC SHOCK			
subjects affected / exposed	2 / 183 (1.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
SINUSITIS			

subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	2 / 183 (1.09%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
UROSEPSIS				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VIRAL INFECTION				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VARICELLA				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
WOUND INFECTION STAPHYLOCOCCAL				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
HYPOKALAEMIA				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DEHYDRATION				

subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	100 MG QD	100 MG BID	50 MG BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 59 (83.05%)	306 / 381 (80.31%)	1 / 1 (100.00%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	10 / 59 (16.95%)	62 / 381 (16.27%)	0 / 1 (0.00%)
occurrences (all)	13	82	0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	3 / 59 (5.08%)	6 / 381 (1.57%)	0 / 1 (0.00%)
occurrences (all)	3	6	0
OEDEMA PERIPHERAL			
subjects affected / exposed	3 / 59 (5.08%)	24 / 381 (6.30%)	0 / 1 (0.00%)
occurrences (all)	3	34	0
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	0 / 59 (0.00%)	4 / 381 (1.05%)	1 / 1 (100.00%)
occurrences (all)	0	6	1
COUGH			
subjects affected / exposed	2 / 59 (3.39%)	15 / 381 (3.94%)	1 / 1 (100.00%)
occurrences (all)	2	18	1
Investigations			
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 59 (0.00%)	6 / 381 (1.57%)	1 / 1 (100.00%)
occurrences (all)	0	10	1
BLOOD PRESSURE INCREASED			
subjects affected / exposed	1 / 59 (1.69%)	27 / 381 (7.09%)	0 / 1 (0.00%)
occurrences (all)	1	35	0
TRANSAMINASES INCREASED			

subjects affected / exposed	7 / 59 (11.86%)	35 / 381 (9.19%)	0 / 1 (0.00%)
occurrences (all)	8	45	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	4 / 59 (6.78%)	33 / 381 (8.66%)	0 / 1 (0.00%)
occurrences (all)	7	49	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 59 (1.69%)	24 / 381 (6.30%)	0 / 1 (0.00%)
occurrences (all)	1	28	0
NEUTROPENIA			
subjects affected / exposed	5 / 59 (8.47%)	30 / 381 (7.87%)	0 / 1 (0.00%)
occurrences (all)	5	34	0
Eye disorders			
CONJUNCTIVITIS			
subjects affected / exposed	3 / 59 (5.08%)	11 / 381 (2.89%)	0 / 1 (0.00%)
occurrences (all)	3	11	0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	3 / 59 (5.08%)	10 / 381 (2.62%)	0 / 1 (0.00%)
occurrences (all)	3	10	0
DIARRHOEA			
subjects affected / exposed	20 / 59 (33.90%)	96 / 381 (25.20%)	0 / 1 (0.00%)
occurrences (all)	36	151	0
DYSPEPSIA			
subjects affected / exposed	3 / 59 (5.08%)	8 / 381 (2.10%)	1 / 1 (100.00%)
occurrences (all)	4	8	1
GASTRITIS			
subjects affected / exposed	5 / 59 (8.47%)	14 / 381 (3.67%)	0 / 1 (0.00%)
occurrences (all)	5	15	0
HAEMORRHOIDS			
subjects affected / exposed	4 / 59 (6.78%)	1 / 381 (0.26%)	0 / 1 (0.00%)
occurrences (all)	4	1	0
NAUSEA			
subjects affected / exposed	3 / 59 (5.08%)	27 / 381 (7.09%)	0 / 1 (0.00%)
occurrences (all)	4	31	0
VOMITING			

subjects affected / exposed	5 / 59 (8.47%)	23 / 381 (6.04%)	0 / 1 (0.00%)
occurrences (all)	9	27	0
Skin and subcutaneous tissue disorders			
SKIN LESION			
subjects affected / exposed	3 / 59 (5.08%)	4 / 381 (1.05%)	0 / 1 (0.00%)
occurrences (all)	3	4	0
RASH			
subjects affected / exposed	3 / 59 (5.08%)	9 / 381 (2.36%)	0 / 1 (0.00%)
occurrences (all)	3	10	0
Renal and urinary disorders			
HYPERTONIC BLADDER			
subjects affected / exposed	0 / 59 (0.00%)	2 / 381 (0.52%)	1 / 1 (100.00%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 59 (1.69%)	17 / 381 (4.46%)	0 / 1 (0.00%)
occurrences (all)	2	25	0
BACK PAIN			
subjects affected / exposed	3 / 59 (5.08%)	30 / 381 (7.87%)	0 / 1 (0.00%)
occurrences (all)	3	35	0
BURSITIS			
subjects affected / exposed	4 / 59 (6.78%)	16 / 381 (4.20%)	0 / 1 (0.00%)
occurrences (all)	5	20	0
OSTEOARTHRITIS			
subjects affected / exposed	3 / 59 (5.08%)	10 / 381 (2.62%)	0 / 1 (0.00%)
occurrences (all)	3	10	0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	3 / 59 (5.08%)	38 / 381 (9.97%)	0 / 1 (0.00%)
occurrences (all)	6	69	0
TENDONITIS			
subjects affected / exposed	4 / 59 (6.78%)	2 / 381 (0.52%)	0 / 1 (0.00%)
occurrences (all)	4	3	0
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	3 / 59 (5.08%)	26 / 381 (6.82%)	0 / 1 (0.00%)
occurrences (all)	4	38	0

INFLUENZA			
subjects affected / exposed	8 / 59 (13.56%)	36 / 381 (9.45%)	0 / 1 (0.00%)
occurrences (all)	15	54	0
NASOPHARYNGITIS			
subjects affected / exposed	3 / 59 (5.08%)	27 / 381 (7.09%)	0 / 1 (0.00%)
occurrences (all)	3	31	0
PHARYNGITIS			
subjects affected / exposed	5 / 59 (8.47%)	16 / 381 (4.20%)	0 / 1 (0.00%)
occurrences (all)	6	19	0
SINUSITIS			
subjects affected / exposed	3 / 59 (5.08%)	26 / 381 (6.82%)	0 / 1 (0.00%)
occurrences (all)	3	37	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	7 / 59 (11.86%)	51 / 381 (13.39%)	1 / 1 (100.00%)
occurrences (all)	8	76	1
URINARY TRACT INFECTION			
subjects affected / exposed	12 / 59 (20.34%)	72 / 381 (18.90%)	0 / 1 (0.00%)
occurrences (all)	32	125	0
Metabolism and nutrition disorders			
HYPERLIPIDAEMIA			
subjects affected / exposed	3 / 59 (5.08%)	3 / 381 (0.79%)	0 / 1 (0.00%)
occurrences (all)	3	3	0
HYPOKALAEMIA			
subjects affected / exposed	3 / 59 (5.08%)	9 / 381 (2.36%)	0 / 1 (0.00%)
occurrences (all)	3	16	0

Non-serious adverse events	150 MG QD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 183 (77.05%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	26 / 183 (14.21%)		
occurrences (all)	31		
General disorders and administration site conditions			
CHEST PAIN			

subjects affected / exposed	0 / 183 (0.00%)		
occurrences (all)	0		
OEDEMA PERIPHERAL			
subjects affected / exposed	7 / 183 (3.83%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences (all)	1		
COUGH			
subjects affected / exposed	8 / 183 (4.37%)		
occurrences (all)	9		
Investigations			
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	2 / 183 (1.09%)		
occurrences (all)	5		
BLOOD PRESSURE INCREASED			
subjects affected / exposed	11 / 183 (6.01%)		
occurrences (all)	11		
TRANSAMINASES INCREASED			
subjects affected / exposed	15 / 183 (8.20%)		
occurrences (all)	16		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	23 / 183 (12.57%)		
occurrences (all)	35		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	13 / 183 (7.10%)		
occurrences (all)	17		
NEUTROPENIA			
subjects affected / exposed	10 / 183 (5.46%)		
occurrences (all)	13		
Eye disorders			
CONJUNCTIVITIS			

subjects affected / exposed	5 / 183 (2.73%)		
occurrences (all)	5		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	3 / 183 (1.64%)		
occurrences (all)	4		
DIARRHOEA			
subjects affected / exposed	60 / 183 (32.79%)		
occurrences (all)	93		
DYSPEPSIA			
subjects affected / exposed	3 / 183 (1.64%)		
occurrences (all)	4		
GASTRITIS			
subjects affected / exposed	8 / 183 (4.37%)		
occurrences (all)	8		
HAEMORRHOIDS			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences (all)	0		
NAUSEA			
subjects affected / exposed	11 / 183 (6.01%)		
occurrences (all)	12		
VOMITING			
subjects affected / exposed	10 / 183 (5.46%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
SKIN LESION			
subjects affected / exposed	2 / 183 (1.09%)		
occurrences (all)	2		
RASH			
subjects affected / exposed	8 / 183 (4.37%)		
occurrences (all)	9		
Renal and urinary disorders			
HYPERTONIC BLADDER			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	10 / 183 (5.46%)		
occurrences (all)	16		
BACK PAIN			
subjects affected / exposed	9 / 183 (4.92%)		
occurrences (all)	11		
BURSITIS			
subjects affected / exposed	5 / 183 (2.73%)		
occurrences (all)	5		
OSTEOARTHRITIS			
subjects affected / exposed	2 / 183 (1.09%)		
occurrences (all)	2		
RHEUMATOID ARTHRITIS			
subjects affected / exposed	10 / 183 (5.46%)		
occurrences (all)	16		
TENDONITIS			
subjects affected / exposed	2 / 183 (1.09%)		
occurrences (all)	2		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	14 / 183 (7.65%)		
occurrences (all)	20		
INFLUENZA			
subjects affected / exposed	18 / 183 (9.84%)		
occurrences (all)	20		
NASOPHARYNGITIS			
subjects affected / exposed	10 / 183 (5.46%)		
occurrences (all)	12		
PHARYNGITIS			
subjects affected / exposed	5 / 183 (2.73%)		
occurrences (all)	6		
SINUSITIS			
subjects affected / exposed	4 / 183 (2.19%)		
occurrences (all)	4		
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed occurrences (all) URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	20 / 183 (10.93%) 29 28 / 183 (15.30%) 45		
Metabolism and nutrition disorders HYPERLIPIDAEMIA subjects affected / exposed occurrences (all) HYPOKALAEMIA subjects affected / exposed occurrences (all)	 1 / 183 (0.55%) 1 2 / 183 (1.09%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2008	The addition of an independent data monitoring committee. Additional vital signs data collection.
18 April 2011	Removed restrictions on male contraception and sperm donation. Described ongoing cardiovascular event adjudication. Updated treatment period to allow investigator to reduce visit frequency to once every 3 months for patients stable on treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported