



Clinical trial results:

Phase III study evaluating two strategies of maintenance, one with pemetrexed in continuous strategy and one according to the response of induction chemotherapy, in non squamous non small cell lung cancer of advanced stage

Summary

EudraCT number	2012-000092-16
Trial protocol	FR
Global end of trial date	30 November 2017

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	IFCT-GFPC-1101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01631136
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 RUE DE LA GRANGE BATELIERE, PARIS, France, 75009
Public contact	Contact, IFCT, 33 1568110545, contact@ifct.fr
Scientific contact	Contact, IFCT, 33 1568110545, contact@ifct.fr

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	29 November 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determinate in patients with metastatic non-squamous non small cell lung cancer without activating EGFR mutation or knowledge of ALK gene rearrangement the benefit in overall survival of a maintenance strategy determined by the response to induction chemotherapy by cisplatin-gemcitabine (continuation maintenance by gemcitabine for patient with objective response and switch maintenance by pemetrexed for patient with stable disease) compared to chemotherapy by cisplatin-pemetrexed followed by a continuation maintenance by pemetrexed.

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 932
Worldwide total number of subjects	932
EEA total number of subjects	932

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)	721
From 65 to 84 years	209
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

932 pts enrolled, 467 in the investigational arm and 465 in the reference arm. 1 patient excluded from analysis because no consent was found for him. The intent-to-treat (ITT) analysis thus deals with 931 pts. 257 patients received a maintenance in the experimental arm and 277 patients in the control arm.

Pre-assignment

Screening details:

Induction chemotherapy: Stage IV non-squamous NSCLC, Age 18-70 years, PS 0 or 1, adequate organ functions, No evidence of EGFR activating mutation or ALK rearrangement, Asymptomatic brain metastases, measurable disease (RECIST1.1). Maintenance: Objective Response (OR) or disease stabilization after induction, PS 0 or 1, Creatinine clearance >45 ml.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Arm

Arm description:

The control arm included 4 induction cycles with Cisplatin 75 mg/m² and Pemetrexed 500 mg/m² given every three weeks, followed by, in the absence of disease progression, a maintenance with Pemetrexed 500 mg/m² every 3 weeks, until progression or unacceptable toxicities. The second-line treatment was left to the investigator's choice.

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Cisplatin 75 mg/m² at day 1 of each cycle. Control arm includes 4 induction cycles of 3 weeks. Cisplatin 1 mg/ml solution for infusion should be diluted before administration. The diluted solution should be administered by intravenous infusion only. When administering, avoid any device containing aluminium that may come into contact with cisplatin.

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

Dosage and administration details:

The dosage of pemetrexed is 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle. During induction chemotherapy, it is given in combination with cisplatin. Cisplatin should be administered 30 min after pemetrexed infusion. During maintenance period, pemetrexed is administered as monotherapy with the same dosage: 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle.

Arm title	Investigational Arm
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Arm description:

The investigational arm consist of a combination of Cisplatin 80 mg/m² every 3 weeks and Gemcitabine

1250 mg/m², on Day 1 and Day 8, every 3 weeks. After 4 cycles, the tumoral assessment by investigators determined the modalities for the maintenance treatment: in case of objective response (OR), continuation maintenance with Gemcitabine 1250 mg/m² given on Day 1 and Day 8 of 21-day cycles until progression or toxicity; in case of Stable Disease (SD), switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression (with folic acid and vitamin B12 supplementation). In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 80 mg/m² at day 1 of each cycle. Investigationanl arm includes 4 induction cycles of 3 weeks in combination with gemcitabine.

CISPLATINE 1 mg/ml solution for infusion should be diluted before administration. The diluted solution should be administered by intravenous infusion only. When administering, avoid any device containing aluminium that may come into contact with cisplatin.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During induction, gemcitabine is given in combination with cisplatin at a dose of 1250mg/m² as a 30 minute intravenous infusion on Days 1 and day 8 followed by one week of rest for a 21 days cycle.

During maintenance, gemcitabine is given as monochemotherapy with the same dosage as induction.

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

Dosage and administration details:

Switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression. In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

The dosage of pemetrexed is 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle. During this maintenance period, pemetrexed is administrated as monotherapy with the same dosage as induction chemotherapy: 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle.

Number of subjects in period 1 ^[1]	Control Arm	Investigational Arm
Started	465	466
Completed	0	0
Not completed	465	466
Patient refusal	15	15
Physician decision	6	14
Adverse event, non-fatal	77	68
Death	37	27

Intercurrent disease	9	5
Progression before study treatment beginning	1	4
Second cancer	-	1
Lack of efficacy	316	326
Protocol deviation	4	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 932 patients were enrolled in the study. 467 in the investigational arm and 465 in the reference arm. One patient was not taken into consideration in the analysis because the patient's consent was lost. The inten-to-treat(ITT) analysis thus deals with 931 patients instead of 932.

Baseline characteristics

Reporting groups

Reporting group title	Control Arm
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Reporting group description:

The control arm included 4 induction cycles with Cisplatin 75 mg/m² and Pemetrexed 500 mg/m² given every three weeks, followed by, in the absence of disease progression, a maintenance with Pemetrexed 500 mg/m² every 3 weeks, until progression or unacceptable toxicities. The second-line treatment was left to the investigator's choice.

Reporting group title	Investigational Arm
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Reporting group description:

The investigational arm consist of a combination of Cisplatin 80 mg/m² every 3 weeks and Gemcitabine 1250 mg/m², on Day 1 and Day 8, every 3 weeks. After 4 cycles, the tumoral assessment by investigators determined the modalities for the maintenance treatment: in case of objective response (OR), continuation maintenance with Gemcitabine 1250 mg/m² given on Day 1 and Day 8 of 21-day cycles until progression or toxicity; in case of Stable Disease (SD), switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression (with folic acid and vitamin B12 supplementation). In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

Reporting group values	Control Arm	Investigational Arm	Total
Number of subjects	465	466	931
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)	361	361	722
From 65-84 years	104	105	209
85 years and over	0	0	0
Adults (65-70 years)	0	0	0
Age continuous Units: years			
median	60.1	59.2	
full range (min-max)	33.5 to 71.0	35.5 to 70.7	-
Gender categorical Units: Subjects			
Female	141	146	287
Male	324	320	644
Performance status Units: Subjects			
PS 0	185	179	364
PS 1	280	285	565
PS 2	0	1	1
Unknown	0	1	1
Smoking Units: Subjects			

Smoker	434	434	868
Non smoker	28	31	59
Unknown	3	1	4
TNM			
Units: Subjects			
M1a	87	95	182
M1b	378	371	749
Brain metastasis			
Units: Subjects			
Yes	109	88	197
No	356	378	734
Histology			
Units: Subjects			
Adenocarcinoma	409	408	817
Other	56	58	114
EGFR			
Units: Subjects			
Undetermined	22	32	54
Mutation	8	9	17
Not performed	51	55	106
Wild-type	384	370	754

End points

End points reporting groups

Reporting group title	Control Arm
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Reporting group description:

The control arm included 4 induction cycles with Cisplatin 75 mg/m² and Pemetrexed 500 mg/m² given every three weeks, followed by, in the absence of disease progression, a maintenance with Pemetrexed 500 mg/m² every 3 weeks, until progression or unacceptable toxicities. The second-line treatment was left to the investigator's choice.

Reporting group title	Investigational Arm
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Reporting group description:

The investigational arm consist of a combination of Cisplatin 80 mg/m² every 3 weeks and Gemcitabine 1250 mg/m², on Day 1 and Day 8, every 3 weeks. After 4 cycles, the tumoral assessment by investigators determined the modalities for the maintenance treatment: in case of objective response (OR), continuation maintenance with Gemcitabine 1250 mg/m² given on Day 1 and Day 8 of 21-day cycles until progression or toxicity; in case of Stable Disease (SD), switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression (with folic acid and vitamin B12 supplementation). In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

Subject analysis set title	Intent-to-treat population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

all patients who were enrolled in the study between july2012 and june 2016, with the exception of one patient for which no consent was found. He is excluded from this analysis. The intent-to-treat(ITT) analysis thus deals with 931 patients.

Subject analysis set title	Intent-to-treat population -Control Arm
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Control ARM Intent-to-treat population : all patients randomised in control arm.

Subject analysis set title	Intent-to-treat population - Investigational Arm
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Intent-to-treat population - Investigational Arm: all patients randomized in investigational arm.

Primary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival is defined as the time from the date of randomisation until death due to any cause. It will be calculated using the Kaplan-Meier method. The comparison between the 2 arms will be performed using a two-sided Log-Rank test.

For patients who do not die, time to death will be censored at the time of last contact.

The analysis of the primary efficacy endpoint will be conducted in ITT population, based on overall survival.

End point type	Primary
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End point timeframe:

Around 20 months

End point values	Control Arm	Investigational Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	465	466		
Units: month				
median (confidence interval 95%)	10.38 (8.87 to 11.63)	10.87 (9.56 to 12.09)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Control Arm v Investigational Arm
Number of subjects included in analysis	931
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Logrank

Secondary: Progression Free Survival

End point title	Progression Free Survival
End point description:	Progression-free survival is defined as the time from randomization to first observation of progression (according to RECIST v1.1) or date of death (from any cause).
End point type	Secondary
End point timeframe:	Around 5 months

End point values	Control Arm	Investigational Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	465	466		
Units: month				
median (confidence interval 95%)	4.53 (4.27 to 5.09)	4.83 (4.5 to 5.09)		

Statistical analyses

Statistical analysis title	Progression Free Survival
Comparison groups	Control Arm v Investigational Arm

Number of subjects included in analysis	931
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	5.1

Secondary: Control and response rate

End point title	Control and response rate
End point description:	
End point type	Secondary
End point timeframe:	
After 4 cycle study treatment	

End point values	Control Arm	Investigational Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	465	466		
Units: percent				
number (not applicable)				
Objective response	159	168		
Disease control	355	330		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment exposure

End point title	Treatment exposure
End point description:	
End point type	Secondary
End point timeframe:	
around 5 months	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety analysis was done on safety population comprising all patients who received at least one dose of induction therapy and assessed by number of patients with at least one adverse event in each arm.

Time Frame: Around 5 months

Adverse event reporting additional description:

Toxicity was assessed and graded using the NCICTC version 4.0.

The maximal grade of adverse events was collected by cycle of treatment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Induction population _control arm
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Reporting group description:

Population including all patients who received at least one dose of induction chemotherapy (CP). The adverse events are reported from cycle1 day1 (C1D1) of induction chemotherapy until the day before the day 1 of maintenance chemotherapy.

Reporting group title	Induction population _Investigational arm
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Reporting group description:

Population including all patients who received at least one dose of induction chemotherapy (CG). From cycle1 day1 (C1D1) of induction chemotherapy until the day before the day1 of maintenance chemotherapy.

Reporting group title	Pemetrexed maintenance population _control arm
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Reporting group description:

Population including all patients who received at least one dose of maintenance chemotherapy with pemetrexed. From cycle1 day1 (C1D1) of maintenance chemotherapy until the day before the day 1 of second line treatment therapy or 30 days after the last dose of maintenance therapy in case of the absence second line therapy.

Reporting group title	Pemetrexed maintenance population _Investigational arm
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Reporting group description:

Population including all patients who received at least one dose of maintenance chemotherapy with pemetrexed in investigational arm. From cycle1 day1 (C1D1) of maintenance chemotherapy until the day before the day 1 of second line treatment therapy or 30 days after the last dose of maintenance therapy in case of the absence second line therapy.

Reporting group title	Gemcitabine maintenance population _Investigationalarm
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Reporting group description:

Population including all patients who received at least one dose of maintenance chemotherapy with gemcitabine in investigational arm. From cycle1 day1 (C1D1) of maintenance chemotherapy until the day before the day 1 of second line treatment therapy or 30 days after the last dose of maintenance therapy in case of the absence second line therapy.

Serious adverse events	Induction population _control arm	Induction population _Investigational arm	Pemetrexed maintenance population _control arm
Total subjects affected by serious adverse events			
subjects affected / exposed	356 / 464 (76.72%)	357 / 453 (78.81%)	108 / 277 (38.99%)
number of deaths (all causes)	367	361	25
number of deaths resulting from	67	56	

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Bronchial carcinoma			
subjects affected / exposed	3 / 464 (0.65%)	5 / 453 (1.10%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Metastases to meninges			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Vascular disorders			
Phlebitis superficial			
subjects affected / exposed	1 / 464 (0.22%)	4 / 453 (0.88%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	12 / 464 (2.59%)	14 / 453 (3.09%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 12	1 / 15	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Peripheral ischaemia			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Shock haemorrhagic			

subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Thrombosis			
subjects affected / exposed	7 / 464 (1.51%)	6 / 453 (1.32%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Venous thrombosis			
subjects affected / exposed	4 / 464 (0.86%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microangiopathy			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Air embolism			

subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Infarction			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Phlebitis			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Arterial thrombosis			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Varices oesophageal			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Peripheral artery thrombosis			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Haematoma			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Surgical and medical procedures			
osteosynthesis			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

General physical health deterioration			
subjects affected / exposed	29 / 464 (6.25%)	17 / 453 (3.75%)	11 / 277 (3.97%)
occurrences causally related to treatment / all	17 / 34	6 / 17	6 / 14
deaths causally related to treatment / all	0 / 8	0 / 6	0 / 6
Asthenia			
subjects affected / exposed	9 / 464 (1.94%)	4 / 453 (0.88%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	5 / 9	3 / 4	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	6 / 464 (1.29%)	8 / 453 (1.77%)	5 / 277 (1.81%)
occurrences causally related to treatment / all	1 / 7	2 / 9	2 / 5
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 1
Oedema peripheral			
subjects affected / exposed	3 / 464 (0.65%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Malaise			
subjects affected / exposed	3 / 464 (0.65%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chilitis			

subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Oedema			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Generalised oedema			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Hyperthermia			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Implant site dehiscence			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Sudden death			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Injection site scar			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site thrombosis			

subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	7 / 464 (1.51%)	7 / 453 (1.55%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 7	2 / 7	0 / 2
deaths causally related to treatment / all	0 / 6	0 / 4	0 / 2
Dyspnoea			
subjects affected / exposed	15 / 464 (3.23%)	8 / 453 (1.77%)	6 / 277 (2.17%)
occurrences causally related to treatment / all	2 / 16	0 / 8	0 / 7
deaths causally related to treatment / all	0 / 6	0 / 2	0 / 3
Haemoptysis			
subjects affected / exposed	1 / 464 (0.22%)	2 / 453 (0.44%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	2 / 464 (0.43%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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

Acute respiratory distress syndrome			
subjects affected / exposed	2 / 464 (0.43%)	3 / 453 (0.66%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 2	1 / 1	0 / 0
Oropharyngeal pain			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	3 / 464 (0.65%)	10 / 453 (2.21%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	2 / 4	6 / 10	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pleural effusion			
subjects affected / exposed	6 / 464 (1.29%)	12 / 453 (2.65%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 6	0 / 15	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	2 / 464 (0.43%)	3 / 453 (0.66%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	2 / 464 (0.43%)	3 / 453 (0.66%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	2 / 464 (0.43%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Chylothorax			

subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Pulmonary congestion			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Hypoxia			
subjects affected / exposed	0 / 464 (0.00%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Dyspnoea exertional			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Psychiatric disorders			
Anxiety			

subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	3 / 464 (0.65%)	4 / 453 (0.88%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Suicidal behaviour			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Psychomotor retardation			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Suicidal ideation			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Depression			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Investigations			
Platelet count decreased			
subjects affected / exposed	10 / 464 (2.16%)	10 / 453 (2.21%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	10 / 11	9 / 10	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemoglobin decreased			
subjects affected / exposed	4 / 464 (0.86%)	7 / 453 (1.55%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	4 / 4	7 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			

subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
C-reactive protein increased			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Splenic injury			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Fracture			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Radiation necrosis			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			

Tachyarrhythmia			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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 disorders			
Cardiac failure			
subjects affected / exposed	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 464 (0.22%)	4 / 453 (0.88%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	2 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	0 / 464 (0.00%)	3 / 453 (0.66%)	0 / 277 (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
Tachycardia			
subjects affected / exposed	0 / 464 (0.00%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 464 (0.22%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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 tamponade			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Cardio-respiratory arrest			
subjects affected / exposed	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Angina pectoris			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 464 (0.00%)	2 / 453 (0.44%)	0 / 277 (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
Headache			
subjects affected / exposed	2 / 464 (0.43%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Hypoglycaemic coma			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			

subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Intracranial pressure increased			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Loss of consciousness			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Hemiplegia			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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 oedema			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Aphasia			

subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Ischaemic stroke			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clonus			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 464 (0.65%)	4 / 453 (0.88%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	3 / 3	2 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bone marrow failure			
subjects affected / exposed	4 / 464 (0.86%)	3 / 453 (0.66%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	5 / 5	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Neutrophil count decreased			

subjects affected / exposed	5 / 464 (1.08%)	4 / 453 (0.88%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	5 / 5	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Pancytopenia			
subjects affected / exposed	2 / 464 (0.43%)	2 / 453 (0.44%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	2 / 2	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Retinal artery occlusion			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness unilateral			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	8 / 464 (1.72%)	14 / 453 (3.09%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	12 / 14	14 / 15	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nausea			
subjects affected / exposed	14 / 464 (3.02%)	17 / 453 (3.75%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	17 / 18	17 / 18	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abdominal pain			
subjects affected / exposed	3 / 464 (0.65%)	5 / 453 (1.10%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	1 / 3	1 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	7 / 464 (1.51%)	4 / 453 (0.88%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	8 / 8	3 / 4	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 464 (0.00%)	2 / 453 (0.44%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Constipation			
subjects affected / exposed	0 / 464 (0.00%)	3 / 453 (0.66%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Melaena			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Abdominal pain upper			

subjects affected / exposed	1 / 464 (0.22%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	3 / 464 (0.65%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	3 / 464 (0.65%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Oesophageal stenosis			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Ascites			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Gastric ulcer			

subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 464 (0.22%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Biliary colic			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			

subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin disorder			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Skin burning sensation			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 464 (0.65%)	18 / 453 (3.97%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	3 / 3	17 / 19	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Urinary retention			
subjects affected / exposed	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Renal failure			
subjects affected / exposed	6 / 464 (1.29%)	10 / 453 (2.21%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	5 / 6	9 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Chronic kidney disease			

subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 464 (0.00%)	4 / 453 (0.88%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 464 (0.43%)	3 / 453 (0.66%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Flank pain			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Neck pain			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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

Polyarthritis			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Infections and infestations			
Infection			
subjects affected / exposed	4 / 464 (0.86%)	4 / 453 (0.88%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 464 (0.43%)	1 / 453 (0.22%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	8 / 464 (1.72%)	6 / 453 (1.32%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	4 / 8	4 / 6	3 / 5
deaths causally related to treatment / all	3 / 3	1 / 2	0 / 0
Pneumonia			
subjects affected / exposed	3 / 464 (0.65%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bronchitis			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infectious colitis			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Pleural infection			

subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 464 (0.22%)	2 / 453 (0.44%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Lung infection			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Meningitis			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Prostate infection			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Localised infection			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Osteomyelitis			

subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Arthritis infective			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Catheter site infection			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Ear infection			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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
Appendicitis			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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	1 / 464 (0.22%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			

subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Hepatitis E			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	0 / 277 (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
Genital herpes			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 464 (0.00%)	0 / 453 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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
Decreased appetite			
subjects affected / exposed	10 / 464 (2.16%)	1 / 453 (0.22%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	8 / 11	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	4 / 464 (0.86%)	4 / 453 (0.88%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 464 (0.00%)	1 / 453 (0.22%)	0 / 277 (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	2 / 464 (0.43%)	0 / 453 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	3 / 464 (0.65%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	2 / 464 (0.43%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acidosis			
subjects affected / exposed	1 / 464 (0.22%)	1 / 453 (0.22%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	1 / 464 (0.22%)	0 / 453 (0.00%)	0 / 277 (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

Serious adverse events	Pemetrexed maintenance population _Investigational arm	Gemcitabine maintenance population _Investigationalarm	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 115 (34.78%)	80 / 142 (56.34%)	
number of deaths (all causes)	10	18	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	2 / 115 (1.74%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to meninges			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Phlebitis superficial			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral ischaemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathy			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Air embolism			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
osteosynthesis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 115 (1.74%)	7 / 142 (4.93%)	
occurrences causally related to treatment / all	1 / 2	4 / 8	
deaths causally related to treatment / all	0 / 0	2 / 4	

Asthenia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza like illness			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chilitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			

subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site dehiscence			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site scar			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site thrombosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 115 (3.48%)	9 / 142 (6.34%)	
occurrences causally related to treatment / all	0 / 4	1 / 11	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemoptysis			
subjects affected / exposed	3 / 115 (2.61%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 115 (0.00%)	4 / 142 (2.82%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	2 / 115 (1.74%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor retardation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic injury			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tachyarrhythmia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 115 (0.87%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemic coma			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clonus			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 115 (1.74%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	3 / 115 (2.61%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness unilateral			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin burning sensation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary retention			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 115 (0.00%)	3 / 142 (2.11%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Infection			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infectious colitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			

subjects affected / exposed	0 / 115 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	2 / 115 (1.74%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 115 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis E			

subjects affected / exposed	1 / 115 (0.87%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acidosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Induction population _control arm	Induction population _Investigational arm	Pemetrexed maintenance population _control arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	446 / 464 (96.12%)	444 / 453 (98.01%)	263 / 277 (94.95%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 464 (1.51%)	8 / 453 (1.77%)	18 / 277 (6.50%)
occurrences (all)	0	0	8
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	192 / 464 (41.38%)	228 / 453 (50.33%)	124 / 277 (44.77%)
occurrences (all)	193	228	215

Pyrexia			
subjects affected / exposed	30 / 464 (6.47%)	40 / 453 (8.83%)	23 / 277 (8.30%)
occurrences (all)	30	42	26
Chest pain			
subjects affected / exposed	37 / 464 (7.97%)	40 / 453 (8.83%)	27 / 277 (9.75%)
occurrences (all)	30	42	38
Oedema peripheral			
subjects affected / exposed	26 / 464 (5.60%)	31 / 453 (6.84%)	54 / 277 (19.49%)
occurrences (all)	26	32	91
Fatigue			
subjects affected / exposed	12 / 464 (2.59%)	15 / 453 (3.31%)	9 / 277 (3.25%)
occurrences (all)	0	0	15
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	94 / 464 (20.26%)	93 / 453 (20.53%)	69 / 277 (24.91%)
occurrences (all)	95	93	102
Cough			
subjects affected / exposed	62 / 464 (13.36%)	75 / 453 (16.56%)	44 / 277 (15.88%)
occurrences (all)	63	75	56
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	59 / 464 (12.72%)	71 / 453 (15.67%)	33 / 277 (11.91%)
occurrences (all)	59	71	70
Weight decreased			
subjects affected / exposed	64 / 464 (13.79%)	62 / 453 (13.69%)	24 / 277 (8.66%)
occurrences (all)	64	63	0
Blood alkaline phosphatase increased			
subjects affected / exposed	34 / 464 (7.33%)	39 / 453 (8.61%)	15 / 277 (5.42%)
occurrences (all)	34	39	24
Alanine aminotransferase increased	Additional description: AE not relevant to the trial		
subjects affected / exposed	15 / 464 (3.23%)	39 / 453 (8.61%)	35 / 277 (12.64%)
occurrences (all)	15	39	80
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 464 (4.53%)	26 / 453 (5.74%)	38 / 277 (13.72%)
occurrences (all)	21	26	85

Blood creatine increased subjects affected / exposed occurrences (all)	13 / 464 (2.80%) 0	14 / 453 (3.09%) 0	7 / 277 (2.53%) 7
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	18 / 464 (3.88%) 18	23 / 453 (5.08%) 23	13 / 277 (4.69%) 13
Neuropathy peripheral subjects affected / exposed occurrences (all)	10 / 464 (2.16%) 0	7 / 453 (1.55%) 0	10 / 277 (3.61%) 13
Paraesthesia subjects affected / exposed occurrences (all)	25 / 464 (5.39%) 26	16 / 453 (3.53%) 16	17 / 277 (6.14%) 28
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	283 / 464 (60.99%) 284	293 / 453 (64.68%) 297	192 / 277 (69.31%) 409
Neutrophil count decreased subjects affected / exposed occurrences (all)	184 / 464 (39.66%) 186	235 / 453 (51.88%) 237	122 / 277 (44.04%) 231
Thrombocytopenia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	108 / 464 (23.28%) 109	222 / 453 (49.01%) 122	66 / 277 (23.83%) 111
Leukopenia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	18 / 464 (3.88%) 18	29 / 453 (6.40%) 29	9 / 277 (3.25%) 15
Lymphopenia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	23 / 464 (4.96%) 23	23 / 453 (5.08%) 23	9 / 277 (3.25%) 22
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	25 / 464 (5.39%) 25	38 / 453 (8.39%) 38	7 / 277 (2.53%) 0

Eye disorders			
Lacrimation increased			
subjects affected / exposed	21 / 464 (4.53%)	2 / 453 (0.44%)	34 / 277 (12.27%)
occurrences (all)	0	0	62
Conjunctivitis			
subjects affected / exposed	13 / 464 (2.80%)	1 / 453 (0.22%)	27 / 277 (9.75%)
occurrences (all)	0	0	63
Eyelid oedema			
subjects affected / exposed	2 / 464 (0.43%)	2 / 453 (0.44%)	9 / 277 (3.25%)
occurrences (all)	0	0	9
Gastrointestinal disorders			
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	220 / 464 (47.41%)	246 / 453 (54.30%)	85 / 277 (30.69%)
occurrences (all)	221	250	134
Vomiting			
subjects affected / exposed	87 / 464 (18.75%)	119 / 453 (26.27%)	47 / 277 (16.97%)
occurrences (all)	88	120	58
Constipation			
subjects affected / exposed	55 / 464 (11.85%)	74 / 453 (16.34%)	26 / 277 (9.39%)
occurrences (all)	55	74	33
Diarrhoea			
subjects affected / exposed	48 / 464 (10.34%)	64 / 453 (14.13%)	26 / 277 (9.39%)
occurrences (all)	49	64	27
Stomatitis			
alternative assessment type: Systematic			
subjects affected / exposed	35 / 464 (7.54%)	14 / 453 (3.09%)	13 / 277 (4.69%)
occurrences (all)	35	14	0
Abdominal pain upper			
subjects affected / exposed	25 / 464 (5.39%)	15 / 453 (3.31%)	16 / 277 (5.78%)
occurrences (all)	25	15	24
Abdominal pain			
subjects affected / exposed	17 / 464 (3.66%)	16 / 453 (3.53%)	13 / 277 (4.69%)
occurrences (all)	0	0	15
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	17 / 464 (3.66%) 17	39 / 453 (8.61%) 39	9 / 277 (3.25%) 13
Rash subjects affected / exposed occurrences (all)	18 / 464 (3.88%) 0	13 / 453 (2.87%) 0	6 / 277 (2.17%) 8
Pruritus subjects affected / exposed occurrences (all)	5 / 464 (1.08%) 0	7 / 453 (1.55%) 0	7 / 277 (2.53%) 8
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	68 / 464 (14.66%) 68	61 / 453 (13.47%) 61	69 / 277 (24.91%) 154
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	27 / 464 (5.82%) 27	29 / 453 (6.40%) 29	19 / 277 (6.86%) 27
Arthralgia subjects affected / exposed occurrences (all)	7 / 464 (1.51%) 8	23 / 453 (5.08%) 24	13 / 277 (4.69%) 20
Bone pain subjects affected / exposed occurrences (all)	13 / 464 (2.80%) 0	16 / 453 (3.53%) 0	7 / 277 (2.53%) 9
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	13 / 464 (2.80%) 0	14 / 453 (3.09%) 0	20 / 277 (7.22%) 25
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	101 / 464 (21.77%) 102	107 / 453 (23.62%) 109	50 / 277 (18.05%) 65
Hyponatraemia subjects affected / exposed occurrences (all)	22 / 464 (4.74%) 30	24 / 453 (5.30%) 26	7 / 277 (2.53%) 0
Hypoalbuminaemia			

subjects affected / exposed	22 / 464 (4.74%)	24 / 453 (5.30%)	10 / 277 (3.61%)
occurrences (all)	22	25	0
Hyperkalaemia			
subjects affected / exposed	23 / 464 (4.96%)	18 / 453 (3.97%)	8 / 277 (2.89%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	17 / 464 (3.66%)	16 / 453 (3.53%)	4 / 277 (1.44%)
occurrences (all)	0	0	9

Non-serious adverse events	Pemetrexed maintenance population _Investigational arm	Gemcitabine maintenance population _Investigational arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 115 (97.39%)	139 / 142 (97.89%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 115 (8.70%)	28 / 142 (19.72%)	
occurrences (all)	3	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	58 / 115 (50.43%)	66 / 142 (46.48%)	
occurrences (all)	101	128	
Pyrexia			
subjects affected / exposed	9 / 115 (7.83%)	23 / 142 (16.20%)	
occurrences (all)	10	32	
Chest pain			
subjects affected / exposed	12 / 115 (10.43%)	14 / 142 (9.86%)	
occurrences (all)	18	21	
Oedema peripheral			
subjects affected / exposed	21 / 115 (18.26%)	19 / 142 (13.38%)	
occurrences (all)	40	22	
Fatigue			
subjects affected / exposed	8 / 115 (6.96%)	12 / 142 (8.45%)	
occurrences (all)	13	23	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	30 / 115 (26.09%)	43 / 142 (30.28%)	
occurrences (all)	42	79	
Cough			
subjects affected / exposed	21 / 115 (18.26%)	32 / 142 (22.54%)	
occurrences (all)	34	46	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	25 / 115 (21.74%)	23 / 142 (16.20%)	
occurrences (all)	41	40	
Weight decreased			
subjects affected / exposed	6 / 115 (5.22%)	10 / 142 (7.04%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 115 (10.43%)	11 / 142 (7.75%)	
occurrences (all)	16	20	
Alanine aminotransferase increased	Additional description: AE not relevant to the trial		
subjects affected / exposed	21 / 115 (18.26%)	24 / 142 (16.90%)	
occurrences (all)	33	38	
Aspartate aminotransferase increased			
subjects affected / exposed	27 / 115 (23.48%)	21 / 142 (14.79%)	
occurrences (all)	45	36	
Blood creatine increased			
subjects affected / exposed	4 / 115 (3.48%)	8 / 142 (5.63%)	
occurrences (all)	4	8	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 115 (1.74%)	9 / 142 (6.34%)	
occurrences (all)	3	11	
Neuropathy peripheral			
subjects affected / exposed	5 / 115 (4.35%)	8 / 142 (5.63%)	
occurrences (all)	8	11	
Paraesthesia			
subjects affected / exposed	11 / 115 (9.57%)	23 / 142 (16.20%)	
occurrences (all)	16	42	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	80 / 115 (69.57%)	112 / 142 (78.87%)	
occurrences (all)	192	236	
Neutrophil count decreased			
subjects affected / exposed	51 / 115 (44.35%)	62 / 142 (43.66%)	
occurrences (all)	122	104	
Thrombocytopenia			
alternative assessment type: Systematic			
subjects affected / exposed	33 / 115 (28.70%)	59 / 142 (41.55%)	
occurrences (all)	59	108	
Leukopenia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 115 (4.35%)	11 / 142 (7.75%)	
occurrences (all)	9	16	
Lymphopenia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 115 (4.35%)	11 / 142 (7.75%)	
occurrences (all)	7	10	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	3 / 115 (2.61%)	5 / 142 (3.52%)	
occurrences (all)	0	0	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	14 / 115 (12.17%)	1 / 142 (0.70%)	
occurrences (all)	23	1	
Conjunctivitis			
subjects affected / exposed	18 / 115 (15.65%)	2 / 142 (1.41%)	
occurrences (all)	38	2	
Eyelid oedema			
subjects affected / exposed	6 / 115 (5.22%)	0 / 142 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Nausea			
alternative assessment type: Systematic			

subjects affected / exposed	38 / 115 (33.04%)	47 / 142 (33.10%)	
occurrences (all)	54	72	
Vomiting			
subjects affected / exposed	19 / 115 (16.52%)	21 / 142 (14.79%)	
occurrences (all)	21	29	
Constipation			
subjects affected / exposed	14 / 115 (12.17%)	12 / 142 (8.45%)	
occurrences (all)	15	18	
Diarrhoea			
subjects affected / exposed	14 / 115 (12.17%)	12 / 142 (8.45%)	
occurrences (all)	16	17	
Stomatitis			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 115 (3.48%)	0 / 142 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	5 / 115 (4.35%)	11 / 142 (7.75%)	
occurrences (all)	7	14	
Abdominal pain			
subjects affected / exposed	3 / 115 (2.61%)	7 / 142 (4.93%)	
occurrences (all)	3	10	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 115 (5.22%)	17 / 142 (11.97%)	
occurrences (all)	9	23	
Rash			
subjects affected / exposed	7 / 115 (6.09%)	4 / 142 (2.82%)	
occurrences (all)	8	4	
Pruritus			
subjects affected / exposed	6 / 115 (5.22%)	2 / 142 (1.41%)	
occurrences (all)	6	2	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	29 / 115 (25.22%)	26 / 142 (18.31%)	
occurrences (all)	52	64	
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	7 / 115 (6.09%) 11	19 / 142 (13.38%) 29	
Arthralgia subjects affected / exposed occurrences (all)	12 / 115 (10.43%) 18	9 / 142 (6.34%) 16	
Bone pain subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 10	7 / 142 (4.93%) 10	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	7 / 115 (6.09%) 9	9 / 142 (6.34%) 9	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	19 / 115 (16.52%) 25	13 / 142 (9.15%) 20	
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 0	2 / 142 (1.41%) 0	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	4 / 115 (3.48%) 0	6 / 142 (4.23%) 0	
Hyperkalaemia subjects affected / exposed occurrences (all)	3 / 115 (2.61%) 0	6 / 142 (4.23%) 0	
Hypocalcaemia subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 9	4 / 142 (2.82%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2012	This 1st substantial modification aims to add investigator centres, to delete the centre of Saint-Brieuc, to modify the rhythm of the evaluations and to clarify the protocol (minor corrections).
07 November 2012	This 2nd substantial amendment aims to : <ul style="list-style-type: none">- Add investigator centres- Change the address of one centre (Toulon CHI)- Decrease the delay between bone radiotherapy and gemcitabine chemotherapy in accordance with the MA.- Clarify the criteria for non-inclusion of brain metastases and superior vena cava syndromes- Correct consent following review by a patient committee
24 September 2013	This 3rd substantial amendment aims to : <ul style="list-style-type: none">- Add and remove investigating centres- Adding details to the protocol: delay in the start of treatment, dose adaptations and dose caps.
24 March 2014	This 4th substantial amendment aims to : <ul style="list-style-type: none">- Add and delete investigating centres- Clarify the protocol: timeline to the start of treatment, dose adaptations and dose caps.
01 December 2015	This 5th substantial amendment aims to : <ul style="list-style-type: none">- Change the principal investigators of 6 centres.- Clarify the management of toxicities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35051725>