Clinical trial results:
A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed plus Best Supportive Care versus Best Supportive Care Immediately Following Induction Treatment with Pemetrexed + Cisplatin for Advanced Non-Squamous Non Small Cell Lung Cancer

Summary

EudraCT number	2008-002155-24
Trial protocol	NL GB PT ES DE FR FI BE IT GR
Global end of trial date	22 November 2017

Results information

Result version number	v1 (current)
This version publication date	06 December 2018
First version publication date	06 December 2018

Trial information

Trial identification

Sponsor protocol code	H3E-EW-S124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00789373
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 12560

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	22 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare maintenance therapy with pemetrexed plus best supportive care (BSC) versus placebo plus BSC, in terms of objective progression-free survival (PFS) time in patients with Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or IV non squamous NSCLC whose disease has not progressed during 4 cycles of pemetrexed + cisplatin induction chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

Best Supportive Care is treatment given with the intent to maximize quality of life. Best Supportive Care excludes any treatment in which the goal is to cure or slow the progression of the study disease. Patients will receive Best Supportive Care as judged by their treating physician. Those therapies considered acceptable include, but are not limited to, palliative radiation to extrathoracic structures, antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and/or nutritional support (enteral or parenteral).

Evidence for comparator: -

Actual start date of recruitment	17 November 2008
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	Netherlands: 48
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Portugal: 38
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	United Kingdom: 71
Country: Number of subjects enrolled	Belgium: 53
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 106
Country: Number of subjects enrolled	Germany: 126
Country: Number of subjects enrolled	Greece: 34
Country: Number of subjects enrolled	Italy: 175
Country: Number of subjects enrolled	Turkey: 33
Country: Number of subjects enrolled	Australia: 26

Country: Number of subjects enrolled	Romania: 55
Country: Number of subjects enrolled	India: 54
Country: Number of subjects enrolled	Canada: 3
Worldwide total number of subjects	939
EEA total number of subjects	823

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)	619
From 65 to 84 years	320
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Entered

Pre-assignment

Screening details:

No Text Entered

Period 1

Period 1 title	Induction Pemetrexed +Cisplatin
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Arm title	Induction Pemetrexed + Cisplatin

Arm description:

Pemetrexed: 500 mg/m^2, intravenous (IV), on Day 1 of each 21-day cycle for 4 cycles. Cisplatin: 75 mg/m^2, IV, on Day 1 of each 21-day cycle for 4 cycles.

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	LY213514
Other name	Alimta
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed: 500 mg/m^2, intravenous (IV), on Day 1 of each 21-day cycle for 4 cycles.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin: 75 mg/m^2, IV, on Day 1 of each 21-day cycle for 4 cycles.

Number of subjects in period 1	Induction Pemetrexed + Cisplatin
Started	939
Completed	540
Not completed	399
Adverse event, serious fatal	19
Physician decision	7
Consent withdrawn by subject	37
Adverse event, non-fatal	64

Death Due to Toxicity	11
Death Due to Procedure	1
Protocol Violation	1
Lost to follow-up	6
Progressive disease	220
Death Due to Study Disease	24
Protocol Entry Criteria Not Met	9

Period 2

Period 2 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed

Arm description:

Following Induction, received 500 mg/m^2 maintenance pemetrexed, IV, on Day 1 of each 21-day cycle plus Best Supportive Care until progressive disease (PD) or treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	LY213514
Other name	Alimta
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed: 500 mg/m^2, maintenance pemetrexed IV, on Day 1 of each 21-day cycle for 4 cycles plus Best Supportive Care until progressive disease (PD) or treatment discontinuation.

Arm title	Pemetrexed + Cisplatin Followed by Placebo

Arm description:

Following Induction, received placebo (normal saline [0.9% sodium chloride]) administered IV on Day 1 of every 21-day cycle plus Best Supportive Care until PD or treatment discontinuation.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo: Normal saline (0.9% sodium chloride) administered IV on Day 1 every 21-day cycle until progressive disease or treatment discontinuation.

Number of subjects in period 2[1]	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo
Started	359	180
Completed	0	0
Not completed	359	180
Adverse event, serious fatal	4	1
Physician decision	4	2
Consent withdrawn by subject	21	8
Adverse event, non-fatal	65	12
Death Due to Toxicity	1	2
Lost to follow-up	2	-
Progressive disease	253	152
Sponsor decision	-	2
Death Due to Study Disease	3	1
Protocol Entry Criteria Not Met	2	-
Participants on-going at data cut-off	4	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 1 participant received maintenance therapy post-induction but was never randomized.

After the Induction Period of pemetrexed and cisplatin, all eligible participants are randomized to one of two treatment arms: maintenance pemetrexed plus best supportive care or placebo and best supportive care.

Baseline characteristics

Reporting groups	
Reporting group title	Induction Pemetrexed +Cisplatin

Reporting group description: -

Reporting group values	Induction Pemetrexed +Cisplatin	Total	
Number of subjects	939	939	
Age categorical Units: Subjects			
Age continuous Units: years			
median	61.3		
full range (min-max)	24.4 to 83.0	-	
Gender categorical Units: Subjects			
Female	362	362	
Male	577	577	
Race/Ethnicity, Customized Units: Subjects			
Asian	59	59	
African	7	7	
Multiple	2	2	
Caucasian	871	871	
Region of Enrollment Units: Subjects			
Portugal	38	38	
Greece	34	34	
Finland	18	18	
Spain	65	65	
Turkey	33	33	
United Kingdom	71	71	
Italy	175	175	
India	54	54	
France	106	106	
Poland	34	34	
Belgium	53	53	
Romania	55	55	
Australia	26	26	
Netherlands	48	48	
Germany	126	126	
Canada	3	3	
Smoking Status Units: Subjects			
Ever Smoker	757	757	
Never Smoker	175	175	

Unknown	7	7	

End points

End points reporting groups

Reporting group title	Induction Pemetrexed + Cisplatin
Reporting group description:	
Pemetrexed: 500 mg/m^2, intravenous (IV), on Day 1 of each 21-day cycle for 4 cycles. Cisplatin: 75 mg/m^2, IV, on Day 1 of each 21-day cycle for 4 cycles.	
Reporting group title	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed
Reporting group description:	
Following Induction, received 500 mg/m^2 maintenance pemetrexed, IV, on Day 1 of each 21-day cycle plus Best Supportive Care until progressive disease (PD) or treatment discontinuation.	
Reporting group title	Pemetrexed + Cisplatin Followed by Placebo
Reporting group description:	
Following Induction, received placebo (normal saline [0.9% sodium chloride]) administered IV on Day 1 of every 21-day cycle plus Best Supportive Care until PD or treatment discontinuation.	

Primary: Investigator-assessed Objective Progression-free Survival (PFS)

End point title	Investigator-assessed Objective Progression-free Survival (PFS)
End point description:	
Investigator-assessed objective PFS was measured from the date of randomization to the first date of objectively determined progressive disease (PD) or death from any cause. For patients not known to have died as of the data cutoff date and who did not have objective PD, PFS was censored at the date of last objective tumor assessment. PD was determined using Response Evaluation Criteria In Solid Tumors (RECIST) criteria. PD = 20% increase in sum of longest diameter of target lesions.	
End point type	Primary
End point timeframe:	
Date of randomization to the date of measured PD or date of death from any cause (up to 19.3 months)	

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359[1]	180[2]		
Units: Months				
median (confidence interval 95%)	4.11 (3.15 to 4.57)	2.83 (2.60 to 3.12)		

Notes:

[1] - All randomized participants

[2] - All randomized participants

Statistical analyses

Statistical analysis title	Investigator Assessed PFS

Statistical analysis description:

900 patients were planned to be enrolled in order to randomize 558 pts to maintenance therapy. This trial was powered for the primary endpoint, PFS (90% power, assuming 238 events with 52% censoring and a PFS Hazard Ratio (HR)=0.65, alpha=0.05). This trial was also powered for a secondary endpoint, OS (93% power, assuming 390 events with 30% censoring and an OS HR=0.70). Alpha was controlled

for both a preliminary analysis (alpha=0.0001) and final analysis of OS (alpha=0.0499).

Comparison groups	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed v Pemetrexed + Cisplatin Followed by Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00006
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.79

Secondary: Independently-assessed Objective Progression-free Survival (PFS)

End point title	Independently-assessed Objective Progression-free Survival (PFS)

End point description:

To further evaluate the robustness of the PFS analysis, Lilly established an independent review of PFS to assess the potential for investigator bias in the determination of objective PD. PFS was measured from the date of randomization to the first date of objectively determined PD or death. For patients alive as of the data cutoff date and who did not have PD, PFS was censored at the date of the last objective tumor assessment. PD was determined using Response Evaluation Criteria In Solid Tumors (RECIST) criteria. PD = 20% increase in sum of longest diameter of target lesions.

Analysis Population Description: Randomized participants with reviewable scan--(316/359 [88%] Maintenance arm and 156/180 [87%] Placebo comparator arm. The majority of unread scans (12.4%) were due to participants not completing 1 cycle of treatment by the data cutoff date (30 June 2010).

End point type	Secondary

End point timeframe:

Date of randomization to first date of measured PD or date of death from any cause (up to 19.3 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	156		
Units: Months				
median (confidence interval 95%)	3.94 (2.96 to 4.24)	2.60 (2.23 to 2.92)		

Statistical analyses

Statistical analysis title	Independently Assessed PFS
Comparison groups	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed v Pemetrexed + Cisplatin Followed by Placebo
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.81

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is the duration from enrollment to death. For patients who are alive, OS is censored at the last contact.

End point type	Secondary

End point timeframe:

Date of randomization to the date of death from any cause up to 39.5 months

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	180		
Units: Months				
median (confidence interval 95%)	13.86 (12.75 to 16.03)	11.01 (9.95 to 12.52)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed v Pemetrexed + Cisplatin Followed by Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0195
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.96

Notes:

[3] - Parameter estimation comment: Unadjusted HR from Cox model with treatment as the only cofactor.

Secondary: Change From Baseline in the EuroQol Instrument (EQ-5D) Index Score

End point title	Change From Baseline in the EuroQol Instrument (EQ-5D) Index Score

End point description:

The EQ-5D is a generic instrument that describes health status in 5 attributes (mobility, self-care, pain/discomfort, anxiety/depression, usual activities) using a three level scale (no problem, some problems, and major problems). These combinations of attributes are converted into a weighted health-state Index Score according to the United Kingdom (UK) population-based algorithm. The possible values for the Index Score range from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension).

Analysis Population Description: Participants who were randomized and completed the EQ-5D at baseline and at least once post-baseline.

End point type	Secondary

End point timeframe:

Baseline randomization through 30-day post-discontinuation visit (up to 19.3 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	153		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline	0.77 (± 0.21)	0.79 (± 0.18)		
Cycle 1 Day 1 (n=265, 132)	0.01 (± 0.15)	-0.01 (± 0.17)		
Cycle 2 Day 1 (n=241, 129)	0.0 (± 0.19)	0.01 (± 0.17)		
Cycle 3 Day 1 (n=160, 83)	0.0 (± 0.15)	0.03 (± 0.17)		
Cycle 4 Day 1 (n=149, 66)	-0.01 (± 0.15)	0.02 (± 0.18)		
Cycle 5 Day 1 (n=108, 48)	0.01 (± 0.16)	0.01 (± 0.22)		
Cycle 6 Day 1 (n=98, 36)	-0.02 (± 0.18)	0.04 (± 0.14)		

Cycle 7 Day 1 (n=73, 21)	0.01 (± 0.20)	0.01 (± 0.13)		
Cycle 8 Day 1 (n=64, 18)	0.01 (± 0.08)	0.05 (± 0.15)		
Cycle 9 Day 1 (n=48, 14)	-0.03 (± 0.20)	0.06 (± 0.18)		
Cycle 10 Day 1 (n=39, 11)	0.0 (± 0.16)	0.08 (± 0.15)		
Cycle 11 Day 1 (n=33, 8)	-0.02 (± 0.19)	0.04 (± 0.17)		
Cycle 12 Day 1 (n=28, 8)	-0.06 (± 0.27)	0.06 (± 0.16)		
Cycle 13 Day 1 (n=15, 3)	-0.01 (± 0.27)	0.0 (± 0.0)		
Cycle 14 Day 1 (n=11, 4)	0.03 (± 0.26)	0.03 (± 0.05)		
Cycle 15 Day 1 (n=12, 3)	-0.07 (± 0.34)	0.01 (± 0.02)		
Cycle 16 Day 1 (n=7, 1)	-0.01 (± 0.36)	0.0 (± 0.0)		
Cycle 17 Day 1 (n=3, 0)	0.32 (± 0.43)	0.0 (± 0.0)		
Cycle 18 Day 1 (n=2, 0)	0.45 (± 0.52)	0.0 (± 0.0)		
30 Day Post-Study Visit (n=82, 51)	-0.13 (± 0.27)	-0.09 (± 0.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol Instrument (EQ-5D) Visual Analog Scale (VAS)

End point title	Change From Baseline in EuroQol Instrument (EQ-5D) Visual Analog Scale (VAS)

End point description:

Patients indicate their present health state through completion of the VAS. Possible scores range from 0 (worst imaginable health state) to 100 (best imaginable health state).

Analysis Population Description: Participants who were randomized and completed the EQ-5D at baseline and at least once post-baseline.

End point type	Secondary

End point timeframe:

Baseline randomization through 30-day post-discontinuation visit (up to 19.3 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	148		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline	71.1 (± 16.6)	71.0 (± 15.8)		
Cycle 1 Day 1 (n=266, 126)	1.65 (± 9.86)	1.42 (± 10.2)		
Cycle 2 Day 1 (n=239, 127)	1.24 (± 11.2)	3.15 (± 13.0)		
Cycle 3 Day 1 (n=162, 81)	1.82 (± 10.9)	4.90 (± 16.9)		
Cycle 4 Day 1 (n=147, 65)	0.69 (± 13.1)	6.15 (± 16.4)		
Cycle 5 Day 1 (n=107, 48)	1.55 (± 12.4)	5.99 (± 13.1)		
Cycle 6 Day 1 (n=98, 36)	3.01 (± 12.5)	5.76 (± 12.9)		
Cycle 7 Day 1 (n=74, 21)	2.7 (± 14.5)	3.98 (± 10.9)		

Cycle 8 Day 1 (n=64, 18)	4.12 (± 14.1)	7.58 (± 14.8)		
Cycle 9 Day 1 (n=47, 14)	4.19 (± 14.2)	7.61 (± 16.7)		
Cycle 10 Day 1 (n=37, 11)	5.14 (± 15.1)	6.23 (± 18.7)		
Cycle 11 Day 1 (n=33, 8)	2.58 (± 14.7)	0.94 (± 15.4)		
Cycle 12 Day 1 (n=27, 8)	2.11 (± 16.0)	4.63 (± 13.1)		
Cycle 13 Day 1 (n=14, 4)	6.29 (± 16.4)	10.0 (± 3.27)		
Cycle 14 Day 1 (n=11, 4)	3.64 (± 18.4)	14.0 (± 4.55)		
Cycle 15 Day 1 (n=10, 3)	8.40 (± 12.9)	12.0 (± 3.46)		
Cycle 16 Day 1 (n=6, 1)	5.83 (± 9.99)	15.0 (± 0.0)		
Cycle 17 Day 1 (n=3, 0)	15.7 (± 21.1)	0.0 (± 0.0)		
Cycle 18 Day 1 (n=2, 0)	5.0 (± 14.1)	0.0 (± 0.0)		
30 days post-study (n=78, 49)	-4.77 (± 17.3)	-3.92 (± 16.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hospitalizations Due to Adverse Events or Requiring Transfusion (Resource Utilization)

End point title	Percentage of Participants With Hospitalizations Due to Adverse Events or Requiring Transfusion (Resource Utilization)

End point description:

End point type	Secondary

End point timeframe:

Baseline randomization through 30-day post-discontinuation visit (up to 19.3 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359[4]	180[5]		
Units: Percentage of Participants				
number (not applicable)				
Hospitalization due to Drug-related Adverse Event	8.4	3.3		
Transfusions Packed Red Blood Cells	12.3	4.4		
Transfusions Whole Blood	1.4	0.6		
Transfusions Platelets	1.4	0.6		
Transfusions Fresh Frozen Plasma	0	0.6		

Notes:

[4] - All randomized participants.

[5] - All randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Non-Serious Adverse Event (AE) During Maintenance Phase

End point title	Percentage of Participants With a Non-Serious Adverse Event (AE) During Maintenance Phase

End point description:

A summary of non-serious AEs is located in the Reported Adverse Event Module.

Analysis Population Description: Randomized population with 2% cut-off threshold for inclusion for 19.3 months and 5% for 49.7 months.

End point type	Secondary

End point timeframe:

Baseline randomization through 30-day post-discontinuation visit (up to 49.7 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	180		
Units: Percentage of Participants				
number (not applicable)				
Non-Serious AEs at 2% Threshold: up to 19.3 Month	59.9	50.6		
Non-Serious AEs at 5% Threshold: up to 49.7 Months	75.5	52.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serious Adverse Events During Maintenance Phase

End point title	Percentage of Participants With Serious Adverse Events During Maintenance Phase

End point description:

A summary of serious adverse events is located in the Reported Adverse Event Module.

Analysis Population Description: Randomized population with all serious adverse events included.

End point type	Secondary

End point timeframe:

Baseline randomization through 30-day post-discontinuation visit (up to 49.7 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	180		
Units: Percentage of Participants				
number (not applicable)				
Serious Adverse Events: up to 19.3 Months	18.9	12.2		
Serious Adverse Events: up to 49.7 Months	26.2	20.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Tumor Response (Response Rate) During Maintenance Phase of Study up to Primary Data Cut-Off

End point title	Percentage of Participants With Objective Tumor Response (Response Rate) During Maintenance Phase of Study up to Primary Data Cut-Off

End point description:

Analysis for combined phases was not performed since response was calculated separately for each phase of study. Response using Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Complete Response (CR)=disappearance of all target lesions; Partial Response(PR)is at least a 30% decrease in sum of longest diameter of target lesions; Progressive Disease(PD) is at least a 20% increase in sum of longest diameter of target lesions; Stable Disease(SD)=no change or small changes that do not meet the above criteria for CR, PR, or PD.

End point type	Secondary

End point timeframe:

Baseline to date of measured progressive disease (up to 19.3 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359[6]	180[7]		
Units: Percentage of Participants				
number (not applicable)	46.2	42.2		

Notes:

[6] - All randomized participants.

[7] - All randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Independently-Assessed Objective

Tumor Response (Response Rate) During Maintenance Phase Up to Primary Data Cut-Off

End point title	Percentage of Participants With Independently-Assessed Objective Tumor Response (Response Rate) During Maintenance Phase Up to Primary Data Cut-Off

End point description:

Response using Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Complete Response (CR)=disappearance of all target lesions; Partial Response (PR) is at least a 30% decrease in sum of longest diameter of target lesions; Progressive Disease (PD) is at least a 20% increase in sum of longest diameter of target lesions; Stable Disease (SD)=no change or small changes that do not meet the above criteria for CR, PR, or PD. Response Rate = (CR+PR)/Participants in Arm*100. Disease Control Rate=(CR+PR+SD)/Number of Participants in Arm*100.

End point type	Secondary

End point timeframe:

Date of randomization to date of measured PD (up to 19.3 months)

End point values	Pemetrexed + Cisplatin Followed by Maintenance Pemetrexed	Pemetrexed + Cisplatin Followed by Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359[8]	180[9]		
Units: Percentage of Participants				
number (confidence interval 95%)				
Response Rate	46.2 (41.0 to 51.6)	42.2 (34.9 to 49.8)		
Disease Control Rate	98.1 (96.0 to 99.2)	94.4 (90.0 to 97.3)		

Notes:

[8] - All randomized participants.

[9] - All randomized participants.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Start of study up to approximately 108 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Induction pemetrexed + cisplatin
Reporting group description: -	
Reporting group title	pemetrexed plus BSC
Reporting group description: -	
Reporting group title	placebo plus BSC
Reporting group description: -	

Serious adverse events	Induction pemetrexed + cisplatin	pemetrexed plus BSC	placebo plus BSC
Total subjects affected by serious adverse events			
subjects affected / exposed	257 / 939 (27.37%)	94 / 359 (26.18%)	36 / 180 (20.00%)
number of deaths (all causes)	46	7	3
number of deaths resulting from adverse events	16	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast cancer			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tumour necrosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
tumour pain			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
Vascular disorders			
arterial thrombosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
arterial thrombosis limb			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
deep vein thrombosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 939 (0.43%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypertension			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
iliac artery thrombosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic limb pain			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
jugular vein distension			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
peripheral ischaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
superior vena cava syndrome			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
superior vena caval occlusion			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
thrombophlebitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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			
catheter removal			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
abortion spontaneous			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed[1]	1 / 362 (0.28%)	0 / 158 (0.00%)	0 / 68 (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
pregnancy			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed[2]	1 / 362 (0.28%)	0 / 158 (0.00%)	0 / 68 (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
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	5 / 939 (0.53%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	7 / 9	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chest pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	7 / 939 (0.75%)	3 / 359 (0.84%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 17	1 / 17	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
death			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	5 / 939 (0.53%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 5	0 / 1	0 / 0
fatigue			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	7 / 939 (0.75%)	3 / 359 (0.84%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	22 / 22	4 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
general physical health deterioration			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
mucosal inflammation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	7 / 939 (0.75%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	10 / 10	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
multi-organ failure			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
non-cardiac chest pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
oedema peripheral			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

pyrexia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	10 / 939 (1.06%)	4 / 359 (1.11%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	4 / 13	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sudden death			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
thrombosis in device			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
testicular pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed[3]	1 / 577 (0.17%)	0 / 201 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
acute pulmonary oedema			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
acute respiratory failure			

alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
aspiration			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
atelectasis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dyspnoea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	15 / 939 (1.60%)	6 / 359 (1.67%)	3 / 180 (1.67%)
occurrences causally related to treatment / all	4 / 26	6 / 12	0 / 4
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
epistaxis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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
haemoptysis			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	3 / 939 (0.32%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemothorax			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoxia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung disorder			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
pleural effusion			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	11 / 939 (1.17%)	3 / 359 (0.84%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	3 / 28	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pleurisy			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pleuritic pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

pneumothorax			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pulmonary embolism			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	28 / 939 (2.98%)	3 / 359 (0.84%)	3 / 180 (1.67%)
occurrences causally related to treatment / all	31 / 63	12 / 14	1 / 7
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
pulmonary hypertension			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
pulmonary oedema			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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
respiratory arrest			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
respiratory failure			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 939 (0.32%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
confusional state			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
depression			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hallucination			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
biopsy pleura			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
blood creatinine decreased			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood creatinine increased			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	3 / 939 (0.32%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood sodium decreased			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
c-reactive protein increased			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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
creatinine renal clearance decreased			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
haemoglobin decreased			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
liver function test abnormal			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
weight decreased			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
fall			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
femur fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
fracture displacement			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
humerus fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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
joint dislocation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
lumbar vertebral fracture			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
pelvic fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
road traffic accident			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
spinal compression fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
splenic rupture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
subdural haematoma			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tracheal obstruction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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

transfusion reaction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
venous injury			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
acute myocardial infarction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (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
arrhythmia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial fibrillation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial tachycardia			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial thrombosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardiac arrest			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 939 (0.32%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 1
cardiac failure congestive			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
cardiac tamponade			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
cardio-respiratory arrest			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 939 (0.32%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
diastolic dysfunction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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

myocardial infarction alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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
myocardial ischaemia alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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
palpitations alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
pericardial effusion alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pericarditis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sinus tachycardia alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
tachyarrhythmia alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
tachycardia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
ventricular fibrillation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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			
cerebellar infarction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
cerebral infarction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cerebral ischaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 939 (0.43%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
cerebrovascular accident			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	6 / 939 (0.64%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	4 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 4	0 / 0	0 / 0
convulsion			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dizziness			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 939 (0.43%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 6	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
encephalopathy			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
facial paresis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
headache			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	5 / 359 (1.39%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 19	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hemiplegia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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

intracranial aneurysm			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic stroke			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (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
loss of consciousness			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
paraesthesia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
paraplegia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
peripheral motor neuropathy			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyramidal tract syndrome			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
speech disorder			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
syncope			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
transient ischaemic attack			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	13 / 939 (1.38%)	11 / 359 (3.06%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	29 / 30	16 / 21	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bone marrow failure			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
febrile bone marrow aplasia			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
febrile neutropenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	12 / 939 (1.28%)	6 / 359 (1.67%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	13 / 13	6 / 6	0 / 0
deaths causally related to treatment / all	3 / 3	0 / 0	0 / 0
leukopenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 939 (0.32%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutropenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	8 / 939 (0.85%)	6 / 359 (1.67%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	9 / 9	8 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombocytopenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	7 / 939 (0.75%)	5 / 359 (1.39%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	9 / 9	8 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
Eye disorders			
cataract			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diabetic retinopathy			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal adhesions			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
abdominal pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 939 (0.32%)	3 / 359 (0.84%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 11	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abdominal pain lower			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abdominal pain upper			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
ascites			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 939 (0.00%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
colitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
constipation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	6 / 939 (0.64%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	7 / 939 (0.75%)	3 / 359 (0.84%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	7 / 9	1 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
diverticular perforation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
dyspepsia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
dysphagia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 939 (0.43%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

gastric haemorrhage			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastric ulcer			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastritis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haematemesis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
ileus			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	3 / 359 (0.84%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
intestinal obstruction			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
large intestine perforation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	24 / 939 (2.56%)	2 / 359 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	39 / 41	5 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutropenic colitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
oesophageal stenosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
pancreatitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
pancreatitis acute			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

rectal haemorrhage			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
retroperitoneal haemorrhage			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
small intestinal obstruction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
stomatitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 939 (0.32%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	29 / 939 (3.09%)	3 / 359 (0.84%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	31 / 36	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
bile duct obstruction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
cholangitis			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
cholecystitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
cholecystitis acute			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
hepatomegaly			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyperbilirubinaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
Skin and subcutaneous tissue disorders			
rash			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
bladder diverticulum			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
incontinence			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
renal failure			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	5 / 939 (0.53%)	4 / 359 (1.11%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	7 / 7	3 / 7	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
renal failure acute			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	7 / 939 (0.75%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	9 / 9	0 / 1	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
renal impairment			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
renal tubular necrosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
urinary retention			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (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

Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
back pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 939 (0.43%)	1 / 359 (0.28%)	4 / 180 (2.22%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bone pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
flank pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
groin pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
musculoskeletal chest pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
musculoskeletal pain			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	2 / 939 (0.21%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myalgia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
osteoporosis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 36	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pain in extremity			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	4 / 939 (0.43%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pathological fracture			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal disorder			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
spondylitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
anal abscess			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
bronchopneumonia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cellulitis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	3 / 359 (0.84%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
device related infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
endocarditis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
erysipelas			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	3 / 359 (0.84%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	0 / 939 (0.00%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
herpes zoster			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lobar pneumonia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (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
lower respiratory tract infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	3 / 939 (0.32%)	2 / 359 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	1 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung abscess			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
lung infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

lung infection pseudomonal alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
neutropenic sepsis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
oral candidiasis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
peritonitis alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
pneumonia alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	17 / 939 (1.81%)	5 / 359 (1.39%)	3 / 180 (1.67%)
occurrences causally related to treatment / all	4 / 25	5 / 8	1 / 3
deaths causally related to treatment / all	1 / 4	1 / 1	0 / 0
pneumonia pneumococcal alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
postoperative wound infection alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
pyelonephritis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyelonephritis acute			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
respiratory tract infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	2 / 359 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
rotavirus infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
scrotal abscess			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed[4]	0 / 577 (0.00%)	0 / 201 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sepsis			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

septic shock			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
staphylococcal infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper respiratory tract infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	2 / 359 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract infection			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dehydration			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	11 / 939 (1.17%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	11 / 12	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diabetes mellitus			
alternative dictionary used: MedDRA 21.0			

subjects affected / exposed	1 / 939 (0.11%)	1 / 359 (0.28%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diabetes mellitus inadequate control			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypercalcaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	0 / 180 (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
hypercreatininaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
hyperglycaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	2 / 939 (0.21%)	0 / 359 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypocalcaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
hypoglycaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	0 / 939 (0.00%)	1 / 359 (0.28%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

hypokalaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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
hyponatraemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	5 / 939 (0.53%)	0 / 359 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
type 2 diabetes mellitus			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 939 (0.11%)	0 / 359 (0.00%)	0 / 180 (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

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

Non-serious adverse events	Induction pemetrexed + cisplatin	pemetrexed plus BSC	placebo plus BSC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	759 / 939 (80.83%)	287 / 359 (79.94%)	117 / 180 (65.00%)
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	30 / 939 (3.19%)	18 / 359 (5.01%)	3 / 180 (1.67%)
occurrences (all)	76	55	14

paraesthesia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	17 / 939 (1.81%)	17 / 359 (4.74%)	13 / 180 (7.22%)
occurrences (all)	76	118	36
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	152 / 939 (16.19%)	76 / 359 (21.17%)	5 / 180 (2.78%)
occurrences (all)	600	295	11
neutropenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	158 / 939 (16.83%)	38 / 359 (10.58%)	3 / 180 (1.67%)
occurrences (all)	340	100	4
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	141 / 939 (15.02%)	51 / 359 (14.21%)	8 / 180 (4.44%)
occurrences (all)	494	325	16
chest pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	44 / 939 (4.69%)	18 / 359 (5.01%)	6 / 180 (3.33%)
occurrences (all)	139	77	13
fatigue			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	181 / 939 (19.28%)	55 / 359 (15.32%)	16 / 180 (8.89%)
occurrences (all)	743	316	61
mucosal inflammation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	50 / 939 (5.32%)	21 / 359 (5.85%)	5 / 180 (2.78%)
occurrences (all)	83	50	9
oedema peripheral			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	42 / 939 (4.47%)	45 / 359 (12.53%)	5 / 180 (2.78%)
occurrences (all)	168	314	18
pyrexia			

alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	46 / 939 (4.90%)	38 / 359 (10.58%)	7 / 180 (3.89%)
occurrences (all)	63	65	7
Gastrointestinal disorders			
constipation			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	131 / 939 (13.95%)	23 / 359 (6.41%)	14 / 180 (7.78%)
occurrences (all)	339	110	47
diarrhoea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	114 / 939 (12.14%)	28 / 359 (7.80%)	7 / 180 (3.89%)
occurrences (all)	175	44	16
nausea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	362 / 939 (38.55%)	69 / 359 (19.22%)	8 / 180 (4.44%)
occurrences (all)	932	286	15
vomiting			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	210 / 939 (22.36%)	42 / 359 (11.70%)	9 / 180 (5.00%)
occurrences (all)	366	78	14
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	67 / 939 (7.14%)	29 / 359 (8.08%)	11 / 180 (6.11%)
occurrences (all)	250	79	26
dyspnoea			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	73 / 939 (7.77%)	43 / 359 (11.98%)	17 / 180 (9.44%)
occurrences (all)	235	201	54
Skin and subcutaneous tissue disorders			
rash			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	48 / 939 (5.11%)	15 / 359 (4.18%)	9 / 180 (5.00%)
occurrences (all)	90	65	13
Musculoskeletal and connective tissue			

disorders back pain alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	31 / 939 (3.30%) 127	23 / 359 (6.41%) 155	7 / 180 (3.89%) 15
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	119 / 939 (12.67%) 316	32 / 359 (8.91%) 91	6 / 180 (3.33%) 21

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2008	Protocol (a): Re-calculated the sample size for the analysis of the Overall Survival (OS) so the trial would be fully powered for Progression Free Survival (PFS) 90% and OS (80%).
20 July 2009	Protocol amendment (b): Re-calculated the power of the OS analysis by increasing the number of patients entering the induction and maintenance treatment periods. The power of OS was increased from 80% to 93% and for PFS, 90% power was maintained.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported