Clinical trial results:
Phase III randomized trial of BIBW 2992 plus weekly paclitaxel versus Investigator's choice of chemotherapy following BIBW 2992 monotherapy in non-small cell lung cancer patients failing previous erlotinib or gefitinib treatment (LUX lung 5)

Summary

EudraCT number	2009-014563-39
Trial protocol	DE FR ES BE FI GB HU IT AT
Global end of trial date	07 January 2016

Results information

Result version number	v1
This version publication date	05 January 2017
First version publication date	05 January 2017

Trial information

Trial identification

Sponsor protocol code	1200.42

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01085136
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	173 Binger Strasse, Ingelheim am Rhein,, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2013
Global end of trial reached?	Yes
Global end of trial date	07 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this randomized, open-label, active-controlled, multi-center trial is to determine the efficacy of continuing BIBW2292 after progression given as an add-on to chemotherapy in patients with Non-small cell lung cancer (NSCLC) Stage IIIb or IV progressing after BIBW 2992 monotherapy compared to chemotherapy alone in this patient population. Patients on both treatment arms received best supportive care in addition to study treatment. Patients enrolled into the trial will be treated and followed until death or lost to follow-up. Additional information on the health-related quality of life (HRQOL) will be collected.

Protection of trial subjects:

All patients were to be informed verbally &in writing by the investigator on the nature of the trial medication & concerning the trial to be performed. Prior to participation in the trial, written informed consent was to be obtained from each patient according to ICH GCP and the regulatory and legal requirements of the participating country. Prior to the study start, the clinical trial protocol (CTP), informed consent form, and patient information were reviewed and approved by the Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs) of the participating centres.

The DMC was responsible for assessing the safety data from Part A and the safety data (and efficacy data if requested) from Part B of the trial, to ensure the overall safety of patients, and to evaluate the risk/benefit profile of the study treatment.

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Finland: 19

Country: Number of subjects enrolled	France: 177
Country: Number of subjects enrolled	Germany: 114
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	India: 12
Country: Number of subjects enrolled	Israel: 36
Country: Number of subjects enrolled	Italy: 107
Country: Number of subjects enrolled	Korea, Republic of: 187
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	China: 153
Country: Number of subjects enrolled	Peru: 5
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Spain: 60
Country: Number of subjects enrolled	Taiwan: 228
Country: Number of subjects enrolled	Ukraine: 16
Country: Number of subjects enrolled	United Kingdom: 52
Worldwide total number of subjects	1302
EEA total number of subjects	618

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)	824
From 65 to 84 years	466
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. The Subjects were not to be entered to trial for part A & not to be further randomised for Part B, if any of the specific entry criteria was violated.

Period 1

Period 1 title	Part A (All subjects)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial, and blinding of trial medication was not implemented.

Arms

Arm title	Afatinib monotherapy (Part A)

Arm description:

Afatinib 50 mg film-coated tablet was orally administered once daily of each 28-day treatment course, with dose reductions to 40 mg/day and 30 mg/day (following the protocol-defined dose reduction scheme).

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib 50 mg film-coated tablet was orally admistered once daily of each 28-day treatment course, with dose reductions to 40 mg/day and 30 mg/day.

Number of subjects in period 1[1]	Afatinib monotherapy (Part A)
Started	1154
Randomized to Part B	206 [2]
Completed	831
Not completed	323
Other reason not defined above	30
Adverse event, non-fatal	223
Refusal to continue trial medication	64
Lost to follow-up	3
Protocol deviation	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on the patients who successfully completed the screening period and received at least one of the trial medication.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This open-label, 2-stage, randomised (in Part B) trial. Subjects who Discontinued Part A were randomized to Part B of the trial. Thus this milestone represent the number of subjects who Discontinued Part A and were randomized to Part B. Completed are the subjects who were randomized to Part B plus the subjects who completed trial as per protocol, had PD, clinical signs and symptoms of progression.

Period 2

Period 2 title	Part B (Part A subjects entered Part B)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial, and blinding of trial medication was not implemented.

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib plus paclitaxel (Part B)

Arm description:

Afatinib 40 mg film-coated tablet dose was orally administered once daily of each 28-day treatment course, with dose reductions to 30 mg/day and 20 mg/day (following the protocol-defined dose reduction scheme) plus paclitaxel 80 mg/m2 administered via intravenous infusion once weekly (7 weeks on/1 week off; 2 dose reductions were allowed following the protocol-defined dose reduction scheme and the current local summary of product characteristics).

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib 40 mg film-coated tablet dose was orally administered once daily of each 28-day treatment course, with dose reductions to 30 mg/day and 20 mg/day

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

Dosage and administration details:

Paclitaxel 80 mg/m2 administered via intravenous infusion once weekly (7 weeks on/1 week off); 2 dose reductions were allowed.

Arm title	Investigators choice of chemotherapy (Part B)

Arm description:

Reference therapy for Part B dose: Depending on schedule Intravenous or oral administration (2 dose reductions were allowed following the protocol defined dose reduction scheme and the current local summary of product characteristics).

Arm type	Active comparator

Investigational medicinal product name	Investigator's choice of chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Depending on schedule Intravenous infusion or oral tablet administration (2 dose reductions were allowed following the protocol defined dose reduction scheme and the current local summary of product characteristics).

Number of subjects in period 2[3]	Afatinib plus paclitaxel (Part B)	Investigators choice of chemotherapy (Part B)
Started	138	68
Completed	87	42
Not completed	51	26
Adverse event, serious fatal	8	3
Other reason not defined above	6	3
Adverse event, non-fatal	21	5
Refusal to continue trial medication	12	7
Not treated	4	8

Notes:

[3] - 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: This open-label, 2-stage, randomized (in Part B) trial. Not all subjects who completed the part A were randomized to Part B but the subjects who discontinued Part A were only randomized to Part B of the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Part A (All subjects)
Reporting group description:	
Treated set, i.e. all patients who were documented to have taken at least 1 dose of afatinib 50 mg in Part A of the trial and all patients who received at least 1 dose of trial medication in Part B.	

Reporting group values	Part A (All subjects)	Total	
Number of subjects	1154	1154	
Age, Customized Units: Participants			

Age Continuous			
Treated set, i.e. all patients who were documented to have taken at least 1 dose of afatinib 50 mg in Part A of the trial and all patients who received at least 1 dose of trial medication in Part B.			
Units: years			
arithmetic mean	60.1		
standard deviation	± 10.9	-	
Gender, Male/Female Units: Participants			
Female	654	654	
Male	500	500	
Race/Ethnicity, Customized Units: Subjects			
Eastern Asian	491	491	
Caucasian	459	459	
Other	29	29	
Unknown	175	175	
Baseline ECOG Units: Subjects			
Baseline ECOG: 0	341	341	
Baseline ECOG: 1	691	691	
Baseline ECOG: 2	122	122	
Smoking history Units: Subjects			
Never smoked	615	615	
<15 pack years & stopped >1 year before diagnosis	132	132	
Other current or ex−smoker	407	407	
Histologic classification Units: Subjects			
Adenocarcinoma	985	985	
Squamous	90	90	
Other	78	78	
Missing	1	1	

End points

End points reporting groups

Reporting group title	Afatinib monotherapy (Part A)

Reporting group description:

Afatinib 50 mg film-coated tablet was orally administered once daily of each 28-day treatment course, with dose reductions to 40 mg/day and 30 mg/day (following the protocol-defined dose reduction scheme).

Reporting group title	Afatinib plus paclitaxel (Part B)

Reporting group description:

Afatinib 40 mg film-coated tablet dose was orally administered once daily of each 28-day treatment course, with dose reductions to 30 mg/day and 20 mg/day (following the protocol-defined dose reduction scheme) plus paclitaxel 80 mg/m2 administered via intravenous infusion once weekly (7 weeks on/1 week off; 2 dose reductions were allowed following the protocol-defined dose reduction scheme and the current local summary of product characteristics).

Reporting group title	Investigators choice of chemotherapy (Part B)

Reporting group description:

Reference therapy for Part B dose: Depending on schedule Intravenous or oral administration (2 dose reductions were allowed following the protocol defined dose reduction scheme and the current local summary of product characteristics).

Primary: Progression free survival (Part B)

End point title	Progression free survival (Part B)

End point description:

Progression free survival (PFS) time as determined by Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 from day of randomization until progression for patients randomised to combination therapy with afatinib plus paclitaxel or to investigator's choice of chemotherapy. Median is calculated from the Kaplan−Meier curve.

Randomized Set: This analysis set consist of all randomised patients irrespective of whether treated or not.

End point type	Primary

End point timeframe:

From randomization until disease progression or death; Up to 32 months

End point values	Afatinib plus paclitaxel (Part B)	Investigators choice of chemotherapy (Part B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138[1]	68[2]		
Units: Months				
median (confidence interval 95%)	5.55 (5.06 to 6.31)	2.89 (1.87 to 3.94)		

Notes:

[1] - Randomized Set

[2] - Randomized Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is calculated from Cox proportional hazard model with treatment as the only factor, stratified by gender and maximum duration of erlotinib or gefitinib (<6 months vs >=6 months).

Comparison groups	Afatinib plus paclitaxel (Part B) v Investigators choice of chemotherapy (Part B)
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [3]
Method	stratified log−rank test
Parameter estimate	Cox proportional hazard
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.85

Notes:

[3] - P−value is calculated from two−sided stratified log−rank test

Secondary: Progression free survival (Part A)

End point title	Progression free survival (Part A)

End point description:

Progression free survival (PFS) as determined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 for Part A. Median is calculated from the Kaplan−Meier curve.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death; Up to 51 months

End point values	Afatinib monotherapy (Part A)			
Subject group type	Reporting group			
Number of subjects analysed	1154[4]			
Units: Months				
median (confidence interval 95%)	3.15 (2.83 to 3.71)			

Notes:

[4] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (part B)

End point title	Overall survival (part B)

End point description:

Overall survival (OS) as determined by the time from randomization to death in part B. Median is

calculated from the Kaplan−Meier curve.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death; Up to 32 months

End point values	Afatinib plus paclitaxel (Part B)	Investigators choice of chemotherapy (Part B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138[5]	68[6]		
Units: Months				
median (confidence interval 95%)	12.25 (10.91 to 14.88)	13.08 (9.86 to 15.64)		

Notes:

[5] - Randomized set

[6] - Randomized set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is calculated from Cox proportional hazard model with treatment as the only factor, stratified by gender and maximum duration of erlotinib or gefitinib (<6 months vs >=6 months).

Comparison groups	Investigators choice of chemotherapy (Part B) v Afatinib plus paclitaxel (Part B)
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7905 [7]
Method	stratified log−rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.44

Notes:

[7] - P−value is calculated from two−sided stratified log−rank test.

Secondary: Objective response (Part A)

End point title	Objective response (Part A)

End point description:

Objective response (complete response [CR], partial response [PR]) of BIBW 2992 monotherapy according to RECIST 1.1 for Part A.

End point type	Secondary

End point timeframe:

Post baseline tumour-imaging was performed atevery 6 weeks thereafter until disease progression; upto 51 months

End point values	Afatinib monotherapy (Part A)			
Subject group type	Reporting group			
Number of subjects analysed	1154[8]			
Units: Percentage of participants				
number (confidence interval 95%)	8.5 (6.9 to 10.3)			

Notes:

[8] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response (Part B)

End point title	Objective response (Part B)

End point description:

Objective response (CR, PR) of BIBW 2992/paclitaxel combination therapy and comparator chemotherapy in Part B after progression in Part A according to RECIST 1.1 .

End point type	Secondary

End point timeframe:

Post baseline tumour-imaging was performed at every 8 weeks thereafter until disease progression; up to 32 Months

End point values	Afatinib plus paclitaxel (Part B)	Investigators choice of chemotherapy (Part B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138[9]	68[10]		
Units: Percentage of participants				
number (confidence interval 95%)	31.2 (23.6 to 39.6)	13.2 (6.2 to 23.6)		

Notes:

[9] - Randomized Set

[10] - Randomized Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio, 95% CI and p−value (two−sided) from logistic regression stratified for maximum treatment duration of prior erlotinib or gefitinib (>=6 months vs <6 months) and gender.

Comparison groups	Afatinib plus paclitaxel (Part B) v Investigators choice of chemotherapy (Part B)

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.357
upper limit	6.543

Secondary: Intensity and incidence of adverse events (AEs) for Part A & Part B.

End point title	Intensity and incidence of adverse events (AEs) for Part A & Part B.

End point description:

Safety of BIBW 2992 as indicated by intensity and incidence of adverse events, graded according to United States National Cancer Institute Common terminology Criteria for Adverse Events (US NCI CTCAE) Version 3.0 both for Part A and Part B.

End point type	Secondary

End point timeframe:

From first administration of treatment until 28 days after last drug administration, upto 51 Months (Part A) and from randomization until 28 days after last drug administration of Trial medication, upto 32 Months (Part B)

End point values	Afatinib monotherapy (Part A)	Afatinib plus paclitaxel (Part B)	Investigators choice of chemotherapy (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1154[11]	134[12]	64[13]	
Units: Percentage of participants				
number (not applicable)				
Grade 1	8.6	4.5	8.3	
Grade 2	28	26.1	26.7	
Grade 3	41.1	44	38.3	
Grade 4	4.9	9.7	6.7	
Grade 5	16.6	12.7	6.7	

Notes:

[11] - Treated Set

[12] - Treated Set

[13] - Treated Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of treatment until 28 days after last drug administration, upto 51 Months (Part A) and from randomization until 28 days after last drug administration of Trial medication, upto 32 Months (Part B).

Adverse event reporting additional description:

Part A-events that started within the period defined by the first administration of afatinib until randomization into Part B or 28 days after the last administration of afatinib, whichever occurred first. Part B-events that started within the period from randomization through 28 days after the last administration of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Afatinib monotherapy (Part A)

Reporting group description:

Afatinib 50 mg film-coated tablet was orally administered once daily of each 28-day treatment course, with dose reductions to 40 mg/day and 30 mg/day (following the protocol-defined dose reduction scheme).

Reporting group title	Afatinib plus paclitaxel (Part B)

Reporting group description:

Afatinib 40 mg film-coated tablet dose was orally administered once daily of each 28-day treatment course, with dose reductions to 30 mg/day and 20 mg/day (following the protocol defined dose reduction scheme) plus paclitaxel 80 mg/m2 administered via intravenous infusion once weekly (7 weeks on/1 week off; 2 dose reductions were allowed following the protocol defined dose reduction scheme and the current local summary of product characteristics).

Reporting group title	Investigators choice of chemotherapy (Part B)

Reporting group description:

Reference therapy for Part B dose: Depending on schedule Intravenous or oral administration (2 dose reductions were allowed following the protocol defined dose reduction scheme and the current local summary of product characteristics).

Serious adverse events	Afatinib monotherapy (Part A)	Afatinib plus paclitaxel (Part B)	Investigators choice of chemotherapy (Part B)
Total subjects affected by serious adverse events			
subjects affected / exposed	471 / 1154 (40.81%)	54 / 134 (40.30%)	19 / 60 (31.67%)
number of deaths (all causes)	206	20	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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

Lung neoplasm			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Malignant ascites			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Malignant neoplasm of pleura			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Malignant neoplasm progression			
subjects affected / exposed	46 / 1154 (3.99%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 46	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 36	0 / 1	0 / 0
Malignant pleural effusion			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Metastases to bone			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Metastases to central nervous system			
subjects affected / exposed	7 / 1154 (0.61%)	3 / 134 (2.24%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 7	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Metastases to meninges			

subjects affected / exposed	2 / 1154 (0.17%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Metastases to pleura			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Metastases to spine			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Metastasis			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Metastatic pain			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Neoplasm progression			
subjects affected / exposed	19 / 1154 (1.65%)	2 / 134 (1.49%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 19	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 12	0 / 2	0 / 1
Non-small cell lung cancer			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Parathyroid tumour benign			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Pericarditis malignant			
subjects affected / exposed	1 / 1154 (0.09%)	1 / 134 (0.75%)	0 / 60 (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
Tumour compression			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	6 / 1154 (0.52%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Haemorrhage			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hypotension			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Neurogenic shock			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Raynaud's phenomenon			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Shock			
subjects affected / exposed	2 / 1154 (0.17%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Thrombosis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Venous thrombosis limb			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
Lung transplant			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Partial lung resection			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Asthenia			
subjects affected / exposed	8 / 1154 (0.69%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 8	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Chest pain			
subjects affected / exposed	8 / 1154 (0.69%)	1 / 134 (0.75%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	5 / 1154 (0.43%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 0
Extravasation			
subjects affected / exposed	0 / 1154 (0.00%)	0 / 134 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	45 / 1154 (3.90%)	7 / 134 (5.22%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	2 / 46	1 / 7	0 / 1
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 0
Gravitational oedema			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hyperthermia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Local swelling			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Malaise			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Mucosal inflammation			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (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
Multi-organ failure			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Oedema			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Pain			

subjects affected / exposed	5 / 1154 (0.43%)	0 / 134 (0.00%)	0 / 60 (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
Performance status decreased			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Pyrexia			
subjects affected / exposed	9 / 1154 (0.78%)	1 / 134 (0.75%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	2 / 9	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
subjects affected / exposed	8 / 1154 (0.69%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Asphyxia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Atelectasis			

subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Choking			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Cough			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Dyspnoea			
subjects affected / exposed	67 / 1154 (5.81%)	5 / 134 (3.73%)	3 / 60 (5.00%)
occurrences causally related to treatment / all	6 / 70	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	7 / 1154 (0.61%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hydrothorax			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hypercapnia			

subjects affected / exposed	0 / 1154 (0.00%)	0 / 134 (0.00%)	1 / 60 (1.67%)
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			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Interstitial lung disease			
subjects affected / exposed	6 / 1154 (0.52%)	1 / 134 (0.75%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	6 / 6	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 1154 (0.09%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Pleural effusion			
subjects affected / exposed	49 / 1154 (4.25%)	3 / 134 (2.24%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 54	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural fibrosis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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 aspiration			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Pneumonitis			

subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	6 / 1154 (0.52%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Productive cough			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	17 / 1154 (1.47%)	4 / 134 (2.99%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 17	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory acidosis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Respiratory arrest			
subjects affected / exposed	1 / 1154 (0.09%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory failure			

subjects affected / exposed	13 / 1154 (1.13%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 13	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 6	0 / 1	0 / 0
Thoracic haemorrhage			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Confusional state			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Depression			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Mental status changes			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Investigations			
Biopsy lymph gland abnormal			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Gene mutation identification test			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Glomerular filtration rate decreased			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Oxygen saturation decreased			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Staphylococcus test positive			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Weight decreased			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Fall			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Femoral neck fracture			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Femur fracture			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Fracture displacement			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Ligament sprain			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Overdose			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Pelvic fracture			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Post procedural complication			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Road traffic accident			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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 left ventricular failure			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Arrhythmia			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Bradycardia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Cardiac failure			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Cardiac tamponade			

subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Cardiopulmonary failure			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Coronary artery disease			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Myocardial infarction			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Pericardial effusion			
subjects affected / exposed	5 / 1154 (0.43%)	0 / 134 (0.00%)	0 / 60 (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
Tachycardia			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Ataxia			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Brain oedema			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Cerebrovascular accident			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Cognitive disorder			
subjects affected / exposed	1 / 1154 (0.09%)	1 / 134 (0.75%)	0 / 60 (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
Dizziness			
subjects affected / exposed	5 / 1154 (0.43%)	0 / 134 (0.00%)	0 / 60 (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
Dysarthria			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Epilepsy			

subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Headache			
subjects affected / exposed	2 / 1154 (0.17%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 1154 (0.00%)	0 / 134 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	3 / 1154 (0.26%)	1 / 134 (0.75%)	0 / 60 (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
Monoplegia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Nervous system disorder			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Reversible ischaemic neurological deficit			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Sciatica			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Seizure			
subjects affected / exposed	6 / 1154 (0.52%)	1 / 134 (0.75%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Speech disorder			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Spinal cord compression			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (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
Syncope			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 1154 (0.35%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	2 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Neutropenia			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
Diplopia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Vision blurred			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	6 / 1154 (0.52%)	2 / 134 (1.49%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 6	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Ascites			
subjects affected / exposed	4 / 1154 (0.35%)	1 / 134 (0.75%)	0 / 60 (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
Constipation			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Diarrhoea			
subjects affected / exposed	59 / 1154 (5.11%)	6 / 134 (4.48%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	65 / 67	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Dysphagia			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Epigastric discomfort			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Gastritis haemorrhagic			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Gingival bleeding			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Haematemesis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Haemorrhoids			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Ileus			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Ileus paralytic			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Intestinal obstruction			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Jejunal perforation			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Nausea			
subjects affected / exposed	8 / 1154 (0.69%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	4 / 9	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 1154 (0.17%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Peritoneal haemorrhage			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			

subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Stomatitis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Vomiting			
subjects affected / exposed	18 / 1154 (1.56%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	15 / 20	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting projectile			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Cholangitis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Cholestasis			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Hepatic failure			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hepatic mass			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hepatic pain			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hepatitis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Liver injury			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Dermatitis acneiform			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Petechiae			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Rash			

subjects affected / exposed	1 / 1154 (0.09%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin erosion			
subjects affected / exposed	0 / 1154 (0.00%)	0 / 134 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin toxicity			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 1154 (0.78%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	8 / 10	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Haematuria			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Renal colic			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	4 / 1154 (0.35%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Back pain			
subjects affected / exposed	11 / 1154 (0.95%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Mobility decreased			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Muscular weakness			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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 chest pain			

subjects affected / exposed	2 / 1154 (0.17%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Neck pain			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Osteonecrosis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Osteoporosis			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Pain in extremity			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Pathological fracture			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Spinal pain			
subjects affected / exposed	2 / 1154 (0.17%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Aspergillus infection			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Bacterial infection			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 1154 (0.17%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Cellulitis			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	3 / 1154 (0.26%)	0 / 134 (0.00%)	0 / 60 (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
Empyema			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Endocarditis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Erysipelas			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Escherichia sepsis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Fungal infection			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Gastroenteritis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Herpes zoster			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Infection			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Infectious pleural effusion			
subjects affected / exposed	1 / 1154 (0.09%)	1 / 134 (0.75%)	0 / 60 (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
Kidney infection			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Laryngitis			

subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Lobar pneumonia			
subjects affected / exposed	2 / 1154 (0.17%)	0 / 134 (0.00%)	0 / 60 (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
Localised infection			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Lower respiratory tract infection			
subjects affected / exposed	5 / 1154 (0.43%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Lung infection			
subjects affected / exposed	11 / 1154 (0.95%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Nasopharyngitis			

subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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
Paronychia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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			
subjects affected / exposed	42 / 1154 (3.64%)	4 / 134 (2.99%)	3 / 60 (5.00%)
occurrences causally related to treatment / all	3 / 46	2 / 5	0 / 3
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 1154 (0.00%)	1 / 134 (0.75%)	0 / 60 (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			
subjects affected / exposed	5 / 1154 (0.43%)	3 / 134 (2.24%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Sepsis			
subjects affected / exposed	5 / 1154 (0.43%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	5 / 1154 (0.43%)	0 / 134 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin bacterial infection			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Staphylococcal infection			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Staphylococcal skin infection			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Upper respiratory tract infection			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (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
Urinary tract infection			
subjects affected / exposed	2 / 1154 (0.17%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 1154 (1.04%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	11 / 14	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	15 / 1154 (1.30%)	1 / 134 (0.75%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	11 / 16	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hypokalaemia			
subjects affected / exposed	4 / 1154 (0.35%)	0 / 134 (0.00%)	0 / 60 (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
Hyponatraemia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hypophosphataemia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hypoproteinaemia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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
Hypovolaemia			
subjects affected / exposed	1 / 1154 (0.09%)	0 / 134 (0.00%)	0 / 60 (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

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

Non-serious adverse events	Afatinib monotherapy (Part A)	Afatinib plus paclitaxel (Part B)	Investigators choice of chemotherapy (Part B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1129 / 1154 (97.83%)	128 / 134 (95.52%)	50 / 60 (83.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	28 / 1154 (2.43%)	8 / 134 (5.97%)	2 / 60 (3.33%)
occurrences (all)	30	19	2
Haemoglobin decreased			
subjects affected / exposed	11 / 1154 (0.95%)	7 / 134 (5.22%)	0 / 60 (0.00%)
occurrences (all)	13	9	0
Weight decreased			
subjects affected / exposed	132 / 1154 (11.44%)	16 / 134 (11.94%)	3 / 60 (5.00%)
occurrences (all)	139	17	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	60 / 1154 (5.20%)	13 / 134 (9.70%)	4 / 60 (6.67%)
occurrences (all)	63	18	7
Dysgeusia			
subjects affected / exposed	25 / 1154 (2.17%)	7 / 134 (5.22%)	4 / 60 (6.67%)
occurrences (all)	25	7	4
Headache			
subjects affected / exposed	56 / 1154 (4.85%)	16 / 134 (11.94%)	6 / 60 (10.00%)
occurrences (all)	63	19	6
Hypoaesthesia			
subjects affected / exposed	6 / 1154 (0.52%)	9 / 134 (6.72%)	5 / 60 (8.33%)
occurrences (all)	6	10	5
Neuropathy peripheral			
subjects affected / exposed	8 / 1154 (0.69%)	16 / 134 (11.94%)	7 / 60 (11.67%)
occurrences (all)	8	18	7
Paraesthesia			
subjects affected / exposed	25 / 1154 (2.17%)	13 / 134 (9.70%)	2 / 60 (3.33%)
occurrences (all)	25	13	3
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 1154 (0.35%)	8 / 134 (5.97%)	2 / 60 (3.33%)
occurrences (all)	4	9	2

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	80 / 1154 (6.93%)	33 / 134 (24.63%)	6 / 60 (10.00%)
occurrences (all)	98	43	6
Leukopenia			
subjects affected / exposed	5 / 1154 (0.43%)	20 / 134 (14.93%)	7 / 60 (11.67%)
occurrences (all)	5	53	18
Neutropenia			
subjects affected / exposed	7 / 1154 (0.61%)	26 / 134 (19.40%)	8 / 60 (13.33%)
occurrences (all)	8	67	15
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	200 / 1154 (17.33%)	47 / 134 (35.07%)	18 / 60 (30.00%)
occurrences (all)	223	68	31
Chest pain			
subjects affected / exposed	82 / 1154 (7.11%)	9 / 134 (6.72%)	2 / 60 (3.33%)
occurrences (all)	87	10	2
Fatigue			
subjects affected / exposed	136 / 1154 (11.79%)	32 / 134 (23.88%)	10 / 60 (16.67%)
occurrences (all)	147	49	11
Mucosal inflammation			
subjects affected / exposed	200 / 1154 (17.33%)	13 / 134 (9.70%)	0 / 60 (0.00%)
occurrences (all)	230	18	0
Oedema peripheral			
subjects affected / exposed	57 / 1154 (4.94%)	12 / 134 (8.96%)	2 / 60 (3.33%)
occurrences (all)	57	14	2
Pyrexia			
subjects affected / exposed	82 / 1154 (7.11%)	18 / 134 (13.43%)	7 / 60 (11.67%)
occurrences (all)	93	21	10
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	90 / 1154 (7.80%)	11 / 134 (8.21%)	4 / 60 (6.67%)
occurrences (all)	100	11	5
Abdominal pain upper			

subjects affected / exposed	65 / 1154 (5.63%)	19 / 134 (14.18%)	4 / 60 (6.67%)
occurrences (all)	71	25	4
Constipation			
subjects affected / exposed	85 / 1154 (7.37%)	22 / 134 (16.42%)	10 / 60 (16.67%)
occurrences (all)	101	25	14
Diarrhoea			
subjects affected / exposed	964 / 1154 (83.54%)	72 / 134 (53.73%)	4 / 60 (6.67%)
occurrences (all)	1894	216	11
Mouth ulceration			
subjects affected / exposed	91 / 1154 (7.89%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences (all)	113	2	0
Nausea			
subjects affected / exposed	252 / 1154 (21.84%)	28 / 134 (20.90%)	14 / 60 (23.33%)
occurrences (all)	309	69	24
Stomatitis			
subjects affected / exposed	303 / 1154 (26.26%)	14 / 134 (10.45%)	2 / 60 (3.33%)
occurrences (all)	372	19	2
Vomiting			
subjects affected / exposed	211 / 1154 (18.28%)	31 / 134 (23.13%)	4 / 60 (6.67%)
occurrences (all)	289	84	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	194 / 1154 (16.81%)	32 / 134 (23.88%)	13 / 60 (21.67%)
occurrences (all)	216	39	13
Dysphonia			
subjects affected / exposed	36 / 1154 (3.12%)	7 / 134 (5.22%)	2 / 60 (3.33%)
occurrences (all)	36	7	2
Dyspnoea			
subjects affected / exposed	194 / 1154 (16.81%)	34 / 134 (25.37%)	11 / 60 (18.33%)
occurrences (all)	205	39	13
Epistaxis			
subjects affected / exposed	151 / 1154 (13.08%)	19 / 134 (14.18%)	3 / 60 (5.00%)
occurrences (all)	183	24	3
Oropharyngeal pain			

subjects affected / exposed	30 / 1154 (2.60%)	10 / 134 (7.46%)	1 / 60 (1.67%)
occurrences (all)	34	11	1
Productive cough			
subjects affected / exposed	47 / 1154 (4.07%)	6 / 134 (4.48%)	4 / 60 (6.67%)
occurrences (all)	52	8	4
Rhinorrhoea			
subjects affected / exposed	61 / 1154 (5.29%)	6 / 134 (4.48%)	4 / 60 (6.67%)
occurrences (all)	66	8	4
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	87 / 1154 (7.54%)	5 / 134 (3.73%)	0 / 60 (0.00%)
occurrences (all)	99	5	0
Alopecia			
subjects affected / exposed	39 / 1154 (3.38%)	47 / 134 (35.07%)	10 / 60 (16.67%)
occurrences (all)	41	48	10
Dry skin			
subjects affected / exposed	164 / 1154 (14.21%)	6 / 134 (4.48%)	0 / 60 (0.00%)
occurrences (all)	185	6	0
Nail disorder			
subjects affected / exposed	41 / 1154 (3.55%)	9 / 134 (6.72%)	2 / 60 (3.33%)
occurrences (all)	49	11	2
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	71 / 1154 (6.15%)	2 / 134 (1.49%)	0 / 60 (0.00%)
occurrences (all)	80	2	0
Pruritus			
subjects affected / exposed	179 / 1154 (15.51%)	13 / 134 (9.70%)	3 / 60 (5.00%)
occurrences (all)	197	15	3
Rash			
subjects affected / exposed	629 / 1154 (54.51%)	30 / 134 (22.39%)	7 / 60 (11.67%)
occurrences (all)	785	41	8
Skin fissures			
subjects affected / exposed	101 / 1154 (8.75%)	10 / 134 (7.46%)	1 / 60 (1.67%)
occurrences (all)	115	14	1
Psychiatric disorders			

Insomnia			
subjects affected / exposed	39 / 1154 (3.38%)	9 / 134 (6.72%)	1 / 60 (1.67%)
occurrences (all)	43	11	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	46 / 1154 (3.99%)	8 / 134 (5.97%)	2 / 60 (3.33%)
occurrences (all)	51	39	3
Back pain			
subjects affected / exposed	94 / 1154 (8.15%)	8 / 134 (5.97%)	5 / 60 (8.33%)
occurrences (all)	99	11	5
Musculoskeletal pain			
subjects affected / exposed	48 / 1154 (4.16%)	8 / 134 (5.97%)	0 / 60 (0.00%)
occurrences (all)	56	13	0
Myalgia			
subjects affected / exposed	17 / 1154 (1.47%)	10 / 134 (7.46%)	7 / 60 (11.67%)
occurrences (all)	28	39	13
Pain in extremity			
subjects affected / exposed	60 / 1154 (5.20%)	8 / 134 (5.97%)	5 / 60 (8.33%)
occurrences (all)	67	9	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	21 / 1154 (1.82%)	7 / 134 (5.22%)	2 / 60 (3.33%)
occurrences (all)	23	9	3
Conjunctivitis			
subjects affected / exposed	79 / 1154 (6.85%)	12 / 134 (8.96%)	0 / 60 (0.00%)
occurrences (all)	99	14	0
Folliculitis			
subjects affected / exposed	86 / 1154 (7.45%)	5 / 134 (3.73%)	0 / 60 (0.00%)
occurrences (all)	100	5	0
Nasopharyngitis			
subjects affected / exposed	35 / 1154 (3.03%)	10 / 134 (7.46%)	2 / 60 (3.33%)
occurrences (all)	42	23	2
Paronychia			
subjects affected / exposed	342 / 1154 (29.64%)	23 / 134 (17.16%)	0 / 60 (0.00%)
occurrences (all)	392	27	0
Pneumonia			

subjects affected / exposed	68 / 1154 (5.89%)	8 / 134 (5.97%)	1 / 60 (1.67%)
occurrences (all)	68	8	1
Rhinitis			
subjects affected / exposed	54 / 1154 (4.68%)	7 / 134 (5.22%)	4 / 60 (6.67%)
occurrences (all)	54	7	4
Upper respiratory tract infection			
subjects affected / exposed	32 / 1154 (2.77%)	7 / 134 (5.22%)	1 / 60 (1.67%)
occurrences (all)	35	8	1
Urinary tract infection			
subjects affected / exposed	62 / 1154 (5.37%)	14 / 134 (10.45%)	1 / 60 (1.67%)
occurrences (all)	76	15	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	304 / 1154 (26.34%)	37 / 134 (27.61%)	10 / 60 (16.67%)
occurrences (all)	318	49	11
Hypokalaemia			
subjects affected / exposed	51 / 1154 (4.42%)	12 / 134 (8.96%)	3 / 60 (5.00%)
occurrences (all)	60	20	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2010	Inclusion criterion 2 was changed by Protocol Amendment 1 to specify that cytotoxic chemotherapy was to include a platinum-based regimen in patients eligible for a platinum-based therapy for advanced or metastatic disease. In addition, a change was made to the wording of the first exemption to inclusion criterion 2, to specify that patients with a known EGFR mutation were eligible for the study after therapy with a TKI without prior chemotherapy. It was also clarified that patients were exempt from the requirements of inclusion criterion 2 if they fulfilled either of the exemption criteria.
04 May 2010	The amendment also specified that potent P-gp inhibitors and inducers were not to be taken by patients participating in the trial and that exemptions to this rule were to be discussed by the Investigator and sponsor.
24 June 2010	The original CTP also stated that after successful pharmacogenetic testing any remaining blood sample material would be destroyed; Protocol Amendment 3 specified that samples would be destroyed within 3 years after the end of the trial.
12 January 2011	Protocol Amendment 4 specified PFS as the primary efficacy endpoint for the trial. This change was based on the results from a previous study (LUX Lung 1, BI trial 1200.23, [P10-12529]) performed in a comparable study population.
05 October 2011	Protocol Amendment 5 specified that an interim analysis was to be conducted when all patients had been treated for at least 12 weeks during Part A of the trial.
17 September 2012	The restrictions for patients receiving afatinib were updated according to recent data. The restriction to avoid P-gp modulators (as implemented by Protocol Amendment 2) was removed and replaced by a general warning that combinations of afatinib with P-gp modulators were to be used with caution. The assessment of adverse events and the clinical evaluation of liver injury were updated according to new corporate standards. The central evaluation of ECG data in Part B was to be stopped after approval of Amendment 6, as previous clinical data showed that afatinib does not have an effect on QTc or other ECG parameters.
18 January 2013	Since the enrolment in Part B was lower than expected, Amendment 7 changed the planned time points for the analysis of PFS and OS. The primary analysis of PFS was to be performed after all randomised patients were followed for at least 6 months, with a target date of 1 Oct 2013.
11 September 2013	The order and categorisation of endpoints was changed for consistency with clinicaltrials.gov-requirements. As secondary endpoints defined were PFS according to RECIST version 1.1 in Part A, OS in Part B, objective response according to RECIST version 1.1 in Part A, and objective response according to RECIST version 1.1 in Part B. Safety and HRQOL were to be assessed as further endpoints, not as secondary endpoints.
06 February 2014	Randomisation within Part B was stopped with Protocol Amendment 9
07 April 2015	Routine assessments were adapted (simplified or shortened) in Protocol Amendment 10 because the primary analysis of PFS had been completed and sufficient data had been collected for the final overall survival analysis. Monitoring was adjusted to an appropriate level.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported