



Clinical trial results:

A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Single-agent Tarceva® (erlotinib) Following Complete Tumor Resection and with or without Adjuvant Chemotherapy in Patients with Stage IB-IIIa Non-small Cell Lung Carcinoma who have EGFR-positive Tumors

Summary

EudraCT number	2005-001747-29
Trial protocol	BE HU DE AT CZ FR GR IT GB ES
Global end of trial date	25 June 2014

Results information

Result version number	v1 (current)
This version publication date	22 February 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	OSI-774-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00373425
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. on behalf of OSI Pharmaceuticals, LLC
Sponsor organisation address	1 Astellas Way, Northbrook, Illinois, United States,
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. on behalf of OSI Pharmaceuticals, LLC, Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. on behalf of OSI Pharmaceuticals, LLC, Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy of single-agent, oral, once daily, erlotinib (150 mg/day) at increasing disease-free survival following complete surgical resection with or without adjuvant chemotherapy in patients who have Epidermal Growth Factor Receptor (EGFR) positive tumors.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki.

Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 November 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	78 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	Austria: 39
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Germany: 93
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Canada: 58
Country: Number of subjects enrolled	Poland: 94

Country: Number of subjects enrolled	Romania: 23
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	Korea, Republic of: 131
Country: Number of subjects enrolled	Taiwan: 42
Country: Number of subjects enrolled	United States: 352
Worldwide total number of subjects	1250
EEA total number of subjects	536

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)	726
From 65 to 84 years	521
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients with stage IB to IIIA epidermal growth factor receptor (EGFR)-positive non-small cell lung cancer (NSCLC) were enrolled globally. 1252 patients were enrolled however 2 patients did not have adequate Health Insurance Portability and Accountability Act (HIPAA) documentation and were removed from the database.

Pre-assignment

Screening details:

Subjects randomized prior to 7 November 2007 comprise the Breached-Protocol Cohort (BPC); those who had not discontinued were offered open-label erlotinib for up to 2 years. Subjects randomized subsequently are referred to as the Randomized Cohort. Data from BPC subjects were analyzed separately and were not considered part of the primary analyses.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	RC: Erlotinib

Arm description:

Participants in the randomized cohort (RC) who received 150 mg/day erlotinib orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.

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

Dosage and administration details:

150 mg/day erlotinib orally

Arm title	RC: Placebo
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Arm description:

Participants in the randomized cohort (RC) who received matching placebo tablets orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.

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

Dosage and administration details:

placebo tablets once a day

Arm title	BPC-NOLC: Erlotinib/Placebo
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Arm description:

The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007

who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and received at least one dose of erlotinib.

Arm type	Breached protocol Cohort
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg/day erlotinib orally

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

Dosage and administration details:

placebo tablets once a day

Arm title	BPC-NOLC: Placebo Only
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Arm description:

The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007 who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and did not receive any erlotinib.

Arm type	Breached protocol Cohort
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo tablets once a day

Arm title	BPC-OLC: Erlotinib
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Arm description:

The BPC open-label cohort (BPC-OLC) includes participants randomized prior to 07 November 2007 who received at least 1 dose of study drug after being randomized, who entered the open-label erlotinib period. Data presented for the BPC-OLC included data from both the blinded period and the open-label erlotinib period.

Arm type	Breached protocol Cohort
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg/day erlotinib orally

Number of subjects in period 1	RC: Erlotinib	RC: Placebo	BPC-NOLC: Erlotinib/Placebo
Started	623	350	134
Received Treatment	612	342	134
Completed	253	197	0
Not completed	370	153	134
Medical/ethical/noncompliance reason	21	9	10
Death	7	-	3
Patient request	35	18	43
Adverse event	191	22	59
Relapse of NSCLC	116	104	19

Number of subjects in period 1	BPC-NOLC: Placebo Only	BPC-OLC: Erlotinib
Started	11	132
Received Treatment	7	132
Completed	0	60
Not completed	11	72
Medical/ethical/noncompliance reason	2	5
Death	1	-
Patient request	6	7
Adverse event	-	34
Relapse of NSCLC	2	26

Baseline characteristics

Reporting groups

Reporting group title	RC: Erlotinib
Reporting group description: Participants in the randomized cohort (RC) who received 150 mg/day erlotinib orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.	
Reporting group title	RC: Placebo
Reporting group description: Participants in the randomized cohort (RC) who received matching placebo tablets orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.	
Reporting group title	BPC-NOLC: Erlotinib/Placebo
Reporting group description: The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007 who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and received at least one dose of erlotinib.	
Reporting group title	BPC-NOLC: Placebo Only
Reporting group description: The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007 who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and did not receive any erlotinib.	
Reporting group title	BPC-OLC: Erlotinib
Reporting group description: The BPC open-label cohort (BPC-OLC) includes participants randomized prior to 07 November 2007 who received at least 1 dose of study drug after being randomized, who entered the open-label erlotinib period. Data presented for the BPC-OLC included data from both the blinded period and the open-label erlotinib period.	

Reporting group values	RC: Erlotinib	RC: Placebo	BPC-NOLC: Erlotinib/Placebo
Number of subjects	623	350	134
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	62 ± 9.28	61.8 ± 9.34	64.4 ± 9.33
Gender categorical Units: Subjects			
Female	257	141	47
Male	366	209	87
Race Units: Subjects			
White	500	279	114
Black	14	11	4
Asian	107	60	15
American Indian/Alaska Native	1	0	1
Other	1	0	0
Eastern Cooperative Oncology Group (ECOG) Performance Status			

ECOG criteria: 0: Fully active. 1: Ambulatory, carry out work of a light or sedentary nature. 2: Ambulatory, capable of all selfcare. 3: Capable of limited selfcare, confined to bed or chair more than 50% of waking hours. 4: Completely disabled, no selfcare, totally confined to bed or chair. 5: Dead.			
Units: Subjects			
Grade 0	385	211	75
Grade 1	230	134	55
Grade 2	6	5	3
Not measured	2	0	1
Cigarette Smoking History			
Units: Subjects			
Never smoked or ≤ 100 cigarettes in lifetime	129	70	19
Former smoker	423	240	103
Current smoker	71	40	12
Histology			
Units: Subjects			
Adenocarcinoma	367	211	73
Squamous cell carcinoma	196	111	48
Undifferentiated large cell	22	8	6
Mixed NSCLC	29	18	5
Other	9	2	2
Extent of Disease at Diagnosis			
Staging is based on the size of the main tumor and whether it has grown into nearby areas, the spread of cancer to nearby lymph nodes and whether the cancer has spread (metastasized) to other organs of the body.			
Units: Subjects			
Stage IA	1	2	1
Stage IB	329	167	64
Stage IIA	42	24	10
Stage IIB	155	99	36
Stage IIIA	93	58	21
Stage IIIB	2	0	2
Stage IV	1	0	0
Adjuvant Chemotherapy			
Units: Subjects			
Yes	315	200	63
No	308	150	71
Epidermal Growth Factor Receptor (EGFR) Mutation Status			
EGFR mutation status: Activating mutation-positive: exon 19 deletion or exon 21 L858R (or both) detected. Wild-type: neither exon 19 deletion nor exon 21 L858R or any other mutation (exon 18, 19, 20 and 21) detected or undetermined. Undetermined: exon 19 deletion or exon 21 L858R (or both) mutation status undetermined. Activating mutation not positive: neither exon 19 deletion nor exon 21 L858R detected or undetermined (includes other mutation positive and other mutation status undetermined).			
Units: Subjects			
Activating mutation-positive	102	59	10
Wild-type	458	245	116
Undetermined	29	16	1
Activating mutation not positive	30	27	5
Not Available	4	3	2
EGFR Gene Amplification			
Analysis of tumor tissue by fluorescent in situ hybridization (FISH), positivity was defined as amplification (EGFR gene to chromosome ratio of ≥ 2 or ≥ 15 EGFR gene copies in $\geq 10\%$ of tumor			

cells) or high polysomy (≥ 4 EGFR gene copies in $\geq 40\%$ of tumor cells) .			
Units: Subjects			
Positive	445	255	84
Negative	167	87	49
Undetermined	11	8	1
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	583	322	123
Hispanic or Latino	40	28	11

Reporting group values	BPC-NOLC: Placebo Only	BPC-OLC: Erlotinib	Total
Number of subjects	11	132	1250
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	62.7	61.8	
standard deviation	± 6.23	± 9.35	-
Gender categorical			
Units: Subjects			
Female	2	57	504
Male	9	75	746
Race			
Units: Subjects			
White	10	111	1014
Black	0	4	33
Asian	1	17	200
American Indian/Alaska Native	0	0	2
Other	0	0	1
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG criteria: 0: Fully active. 1: Ambulatory, carry out work of a light or sedentary nature. 2: Ambulatory, capable of all selfcare. 3: Capable of limited selfcare, confined to bed or chair more than 50% of waking hours. 4: Completely disabled, no selfcare, totally confined to bed or chair. 5: Dead.			
Units: Subjects			
Grade 0	5	77	753
Grade 1	6	54	479
Grade 2	0	1	15
Not measured	0	0	3
Cigarette Smoking History			
Units: Subjects			
Never smoked or ≤ 100 cigarettes in lifetime	1	19	238
Former smoker	9	104	879
Current smoker	1	9	133
Histology			
Units: Subjects			
Adenocarcinoma	3	76	730
Squamous cell carcinoma	8	49	412
Undifferentiated large cell	0	4	40
Mixed NSCLC	0	1	53

Other	0	2	15
Extent of Disease at Diagnosis			
Staging is based on the size of the main tumor and whether it has grown into nearby areas, the spread of cancer to nearby lymph nodes and whether the cancer has spread (metastasized) to other organs of the body.			
Units: Subjects			
Stage IA	0	0	4
Stage IB	4	80	644
Stage IIA	1	9	86
Stage IIB	4	23	317
Stage IIIA	1	17	190
Stage IIIB	0	3	7
Stage IV	1	0	2
Adjuvant Chemotherapy			
Units: Subjects			
Yes	5	68	651
No	6	64	599
Epidermal Growth Factor Receptor (EGFR) Mutation Status			
EGFR mutation status: Activating mutation-positive: exon 19 deletion or exon 21 L858R (or both) detected. Wild-type: neither exon 19 deletion nor exon 21 L858R or any other mutation (exon 18, 19, 20 and 21) detected or undetermined. Undetermined: exon 19 deletion or exon 21 L858R (or both) mutation status undetermined. Activating mutation not positive: neither exon 19 deletion nor exon 21 L858R detected or undetermined (includes other mutation positive and other mutation status undetermined).			
Units: Subjects			
Activating mutation-positive	0	16	187
Wild-type	11	107	937
Undetermined	0	1	47
Activating mutation not positive	0	6	68
Not Available	0	2	11
EGFR Gene Amplification			
Analysis of tumor tissue by fluorescent in situ hybridization (FISH), positivity was defined as amplification (EGFR gene to chromosome ratio of ≥ 2 or ≥ 15 EGFR gene copies in $\geq 10\%$ of tumor cells) or high polysomy (≥ 4 EGFR gene copies in $\geq 40\%$ of tumor cells) .			
Units: Subjects			
Positive	8	100	892
Negative	3	32	338
Undetermined	0	0	20
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	11	124	1163
Hispanic or Latino	0	8	87

End points

End points reporting groups

Reporting group title	RC: Erlotinib
Reporting group description: Participants in the randomized cohort (RC) who received 150 mg/day erlotinib orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.	
Reporting group title	RC: Placebo
Reporting group description: Participants in the randomized cohort (RC) who received matching placebo tablets orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.	
Reporting group title	BPC-NOLC: Erlotinib/Placebo
Reporting group description: The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007 who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and received at least one dose of erlotinib.	
Reporting group title	BPC-NOLC: Placebo Only
Reporting group description: The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007 who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and did not receive any erlotinib.	
Reporting group title	BPC-OLC: Erlotinib
Reporting group description: The BPC open-label cohort (BPC-OLC) includes participants randomized prior to 07 November 2007 who received at least 1 dose of study drug after being randomized, who entered the open-label erlotinib period. Data presented for the BPC-OLC included data from both the blinded period and the open-label erlotinib period.	

Primary: Disease Free Survival (DFS)

End point title	Disease Free Survival (DFS) ^[1]
End point description: DFS is the time from the date of randomization until the first day non-small cell lung cancer (NSCLC) relapse is documented by radiological exam and/or biopsy, or until death in the absence of relapse. After randomization, NSCLC relapse was based on radiological evidence or biopsy, as determined by the investigator. Participants without a DFS event were censored on the last adequate radiological assessment date. 99999 represents data not estimable.	
End point type	Primary
End point timeframe: Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and yearly thereafter until the data cut-off date of 08 April 2013 (maximum time on follow-up was 64 months).	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	350		
Units: months				
median (confidence interval 95%)	50.5 (44.7 to 99999)	48.2 (36 to 99999)		

Statistical analyses

Statistical analysis title	Unstratified analysis
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Statistical analysis description:

The null hypothesis that DFS distributions of the 2 arms were equivalent was tested using an unstratified 2-sided log-rank test at the 0.05 level. The primary analysis of DFS was performed when at least 410 events had accrued. If the result of the primary analysis of DFS was statistically significant favoring the erlotinib treatment arm, the null hypothesis of no treatment difference of key secondary efficacy variables was tested under a hierarchical testing procedure.

Comparison groups	RC: Erlotinib v RC: Placebo
Number of subjects included in analysis	973
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3235 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.741
upper limit	1.104

Notes:

[2] - If the primary analysis of DFS was not statistically significant, the hierarchical testing procedure would stop and all key secondary efficacy analyses would be nonsignificant; any further analysis of these outcomes would be considered exploratory.

Primary: Disease Free Survival (DFS)

End point title	Disease Free Survival (DFS) ^[3]
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End point description:

DFS is the time from the date of randomization until the first day that non-small cell lung cancer (NSCLC) relapse is documented by radiological exam and/or biopsy, or until death in the absence of relapse. After randomization, NSCLC relapse was based on radiological evidence or biopsy, as determined by the investigator. Participants without a DFS event were censored on the last adequate radiological assessment date.

End point type	Primary
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End point timeframe:

Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and yearly thereafter until the data cutoff date of 11 June 2014 (maximum time on follow-up was 78 months).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	350		
Units: months				
median (confidence interval 95%)	55 (47 to 64.5)	56.2 (39.7 to 65.6)		

Statistical analyses

Statistical analysis title	Unstratified Analysis
Statistical analysis description:	
The null hypothesis that DFS distributions of the 2 arms were equivalent was tested using an unstratified 2-sided log-rank test at the 0.05 level.	
Comparison groups	RC: Erlotinib v RC: Placebo
Number of subjects included in analysis	973
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.562
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.144

Notes:

[4] - Updated exploratory analyses based on a data cutoff date of 11 June 2014.

Secondary: Overall Survival

End point title	Overall Survival ^[5]
End point description:	
Overall survival was defined as the time from the date of randomization until the documented date of death. Participants who were still alive were censored on the last day they were known to be alive. The overall survival data were not mature; 99999 represents data not estimable.	
End point type	Secondary
End point timeframe:	
Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and yearly thereafter until the data cut-off date of 08 April 2013 (maximum time on follow-up was 64 months).	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	350		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival ^[6]
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End point description:

Overall survival was defined as the time from the date of randomization until the documented date of death. Participants who were still alive were censored on the last day they were known to be alive. The overall survival data were not mature; 99999 represents data not estimable.

End point type	Secondary
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End point timeframe:

Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and yearly thereafter until the data cut-off date of 11 June 2014 (maximum time on follow-up was 78 months).

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	350		
Units: months				
median (confidence interval 95%)	99999 (77.9 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free Survival in Participants With EGFR Mutation - Positive Tumors

End point title	Disease-free Survival in Participants With EGFR Mutation - Positive Tumors ^[7]
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End point description:

Disease-free survival (DFS) is the time from the date of randomization until the first day NSCLC relapse is documented by radiological exam and/or biopsy, or until death in the absence of relapse. After randomization, NSCLC relapse was based on radiological evidence or biopsy, as determined by the investigator. Participants without a DFS event were censored on the last adequate radiological assessment date. Activating EGFR mutation-positive is defined as exon 19 deletion or exon 21 L858R (or both) detected.

End point type	Secondary
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End point timeframe:

Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and yearly thereafter until the data cut-off date of 08 April 2013 (maximum time on follow-up was 64 months).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102 ^[8]	59 ^[9]		
Units: months				
median (confidence interval 95%)	46.4 (39.8 to 99999)	28.5 (16.7 to 99999)		

Notes:

[8] - Randomized cohort full analysis set participants who are EGFR mutation positive

[9] - Randomized cohort full analysis set participants who are EGFR mutation positive

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free Survival in Participants With EGFR Mutation - Positive Tumors

End point title	Disease-free Survival in Participants With EGFR Mutation - Positive Tumors ^[10]
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End point description:

Disease-free survival (DFS) is the time from the date of randomization until the first day NSCLC relapse is documented by radiological exam and/or biopsy, or until death in the absence of relapse. After randomization, NSCLC relapse was based on radiological evidence or biopsy, as determined by the investigator. Participants without a DFS event were censored on the last adequate radiological assessment date. Activating EGFR mutation-positive is defined as exon 19 deletion or exon 21 L858R (or both) detected.

99999 represents data not estimable.

End point type	Secondary
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End point timeframe:

Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and yearly thereafter until the data cut-off date of 11 June 2014 (maximum time on follow-up was 78 months).

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102 ^[11]	59 ^[12]		
Units: months				
median (confidence interval 95%)	47.8 (39.8 to 60.8)	28.5 (16.7 to 61.4)		

Notes:

[11] - Randomized cohort full analysis set participants who are EGFR mutation positive

[12] - Randomized cohort full analysis set participants who are EGFR mutation positive

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in Participants With EGFR Mutation - Positive Tumors

End point title	Overall Survival in Participants With EGFR Mutation - Positive Tumors ^[13]
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End point description:

Overall survival is defined as the time from the date of randomization until the documented date of death. Participants who were still alive were censored on the last day they were known to be alive. Activating EGFR mutation-positive is defined as exon 19 deletion or exon 21 L858R (or both) detected. The overall survival data were not mature; 99999 represents data not estimable.

End point type	Secondary
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End point timeframe:

Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and yearly thereafter until the data cut-off date of 08 April 2013 (maximum time on follow-up was 64 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102 ^[14]	59 ^[15]		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (55.4 to 99999)		

Notes:

[14] - Randomized cohort full analysis participants who were EGFR mutation positive

[15] - Randomized cohort full analysis participants who were EGFR mutation positive

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in Participants With EGFR Mutation - Positive Tumors

End point title	Overall Survival in Participants With EGFR Mutation - Positive Tumors ^[16]
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End point description:

Overall survival is defined as the time from the date of randomization until the documented date of death. Participants who were still alive were censored on the last day they were known to be alive. Activating EGFR mutation-positive is defined as exon 19 deletion or exon 21 L858R (or both) detected. The overall survival data were not mature; 99999 represents data not estimable.

End point type	Secondary
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End point timeframe:

Every 3 months during active phase and every 6 months during long term follow-up up to 5 years and

yearly thereafter until the data cut-off date of 11 June 2014 (maximum time on follow-up was 78 months).

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102 ^[17]	59 ^[18]		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[17] - Randomized cohort full analysis participants who were EGFR mutation positive

[18] - Randomized cohort full analysis participants who were EGFR mutation positive

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs) ^[19]
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End point description:

An AE was defined as any untoward medical occurrence in a study participant and did not necessarily have a causal relationship with study treatment.

An AE was considered serious if it resulted in death, a life-threatening situation, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect in the offspring of a participant, other important medical events, or is on the Astellas Always Serious List.

A drug-related AE was any AE with at least a possible relationship to study treatment as assessed by the investigator. Severity was graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v3.0, where Grade 1=Mild AE; Grade=2 Moderate AE; Grade 3=Severe AE; Grade 4=Life-threatening or disabling; Grade 5=Death related to AE. AEs leading to death include deaths that occurred more than 30 days after the last dose of study drug.

End point type	Secondary
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End point timeframe:

From the date of first dose of study drug until 30 days after the last dose. The median time on treatment was 11.9 months for erlotinib and 21.9 months for placebo. Data are based off the 11 June 2014 data cut-off date.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data from the BPC participants were analyzed separately and were not included in the assessments of primary or secondary endpoints in the randomized cohort and were not considered part of the primary analyses.

End point values	RC: Erlotinib	RC: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	611 ^[20]	343 ^[21]		
Units: participants				
Any adverse event (AE)	599	307		
Grade 3 or higher adverse event	279	96		
Serious adverse event (SAE)	118	79		

AE leading to discontinuation of study drug	205	29		
AE leading to death	14	5		
AE leading to dose reduction	150	9		
AE leading to dose interruption	114	23		
AE leading to dose interruption and reduction	156	5		
Drug-related AE	572	181		
Drug-related serious AE	15	5		
Drug-related AE leading to discontinuation	163	8		

Notes:

[20] - Safety analysis set

[21] - Safety analysis set; includes 1 subject assigned to erlotinib who received placebo in error

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until 30 days after the last dose. Maximum time on treatment for the Randomized Cohort was 24 months; maximum time on treatment for the BPC was 13 months on blinded study drug and 26 months on open-label erlotinib.

Adverse event reporting additional description:

One participant in the Randomized Cohort assigned to the erlotinib arm received placebo instead due to a dispensing error and is included in the placebo group for safety analyses. For the Breached Protocol Cohort safety analyses are based on the total no open-label and open-label populations.

Safety data are based on the 11 June 2014 cut-off date.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	RC: Erlotinib
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Reporting group description:

Participants in the randomized cohort (RC) who received 150 mg/day erlotinib orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.

Reporting group title	RC: Placebo
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Reporting group description:

Participants in the randomized cohort (RC) who received matching placebo tablets orally for 2 years or until relapse, death, participant request or investigator decision to discontinue study drug, or intolerable toxicity.

Reporting group title	BPC-NOLC: Erlotinib/Placebo
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Reporting group description:

The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007 who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and received at least one dose of erlotinib.

Reporting group title	BPC-NOLC: Placebo Only
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Reporting group description:

The BPC no open-label cohort (BPC-NOLC) includes participants randomized prior to 07 November 2007 who did not participate in the open-label erlotinib period and who were previously randomized to receive either erlotinib or placebo in the blinded period, and did not receive any erlotinib.

Reporting group title	BPC-OLC: Erlotinib
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Reporting group description:

The BPC open-label cohort (BPC-OLC) includes participants randomized prior to 07 November 2007 who received at least 1 dose of study drug after being randomized, who entered the open-label erlotinib period. Data presented for the BPC-OLC included data from both the blinded period and the open-label erlotinib period.

Serious adverse events	RC: Erlotinib	RC: Placebo	BPC-NOLC: Erlotinib/Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	118 / 611 (19.31%)	79 / 343 (23.03%)	21 / 134 (15.67%)
number of deaths (all causes)	205	108	61
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 611 (0.16%)	5 / 343 (1.46%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Cancer pain			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Conjunctival neoplasm			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Laryngeal cancer			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	5 / 611 (0.82%)	3 / 343 (0.87%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Malignant ascites			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Malignant melanoma			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	4 / 611 (0.65%)	3 / 343 (0.87%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 3	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Neurilemmoma			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Prostate cancer			
subjects affected / exposed	3 / 611 (0.49%)	1 / 343 (0.29%)	0 / 134 (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
Prostate cancer stage I			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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 cell carcinoma stage unspecified			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Sarcoma			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Small cell lung cancer stage unspecified			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Throat cancer			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Thyroid cancer			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Thyroid neoplasm			

subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Tonsil cancer			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Uterine cancer			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Aortic occlusion			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Cardiovascular insufficiency			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Hypertension			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Hypotension			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Temporal arteritis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 611 (0.49%)	1 / 343 (0.29%)	0 / 134 (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
Chest pain			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Death			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Fatigue			
subjects affected / exposed	2 / 611 (0.33%)	1 / 343 (0.29%)	0 / 134 (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
General physical health deterioration			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Multi-organ failure			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Pain			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Performance status decreased			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterovaginal prolapse			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apnoea			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Bronchial fistula			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial hyperreactivity			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	0 / 611 (0.00%)	3 / 343 (0.87%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	6 / 611 (0.98%)	5 / 343 (1.46%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 6	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epistaxis			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Hydrothorax			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 611 (0.33%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleural fibrosis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Pulmonary embolism			
subjects affected / exposed	3 / 611 (0.49%)	5 / 343 (1.46%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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 granuloma			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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 failure			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Inappropriate affect			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Blood creatinine increased			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Ankle fracture			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Bronchial anastomosis complication			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Clavicle fracture			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Concussion			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	3 / 611 (0.49%)	1 / 343 (0.29%)	0 / 134 (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
Femur fracture			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Hip fracture			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			

subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Laceration			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polytraumatism			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Post procedural haematoma			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative fever			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Rib fracture			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Suture rupture			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rathke's cleft cyst			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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

Angina pectoris			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Arrhythmia			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Coronary artery disease			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			

subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Myocardial infarction			
subjects affected / exposed	3 / 611 (0.49%)	0 / 343 (0.00%)	0 / 134 (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
Pericardial effusion			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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			
Balance disorder			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain mass			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral artery embolism			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	3 / 611 (0.49%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphasia			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Epilepsy			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Facial paresis			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	2 / 611 (0.33%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	3 / 611 (0.49%)	4 / 343 (1.17%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IIIrd nerve paralysis			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Memory impairment			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Monoparesis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Neuralgia			

subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Sudden onset of sleep			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 611 (0.65%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Lymphadenopathy			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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			
Deafness			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Deafness neurosensory			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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

Retinal haemorrhage			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 611 (0.16%)	3 / 343 (0.87%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	4 / 611 (0.65%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	4 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Dysphagia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Enteritis			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula			

subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Gastric dysplasia			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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 haemorrhage			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Gingival bleeding			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Haematemesis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	0 / 611 (0.00%)	1 / 343 (0.29%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Peptic ulcer perforation			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Subileus			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Tooth resorption			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Vomiting			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Cholecystitis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Cholecystitis acute			

subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Jaundice			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Rash			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Nephrolithiasis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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 acute			
subjects affected / exposed	4 / 611 (0.65%)	0 / 343 (0.00%)	0 / 134 (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
Urethral obstruction			

subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Urinary incontinence			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Endocrine disorders			
Thyroid cyst			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Bone pain			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Flank pain			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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

Intervertebral disc protrusion			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Muscle haemorrhage			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Muscular weakness			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Osteoarthritis			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Spondylolisthesis acquired			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 611 (0.16%)	2 / 343 (0.58%)	0 / 134 (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
Arthritis infective			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 611 (0.33%)	1 / 343 (0.29%)	0 / 134 (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
Bronchitis acute			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Clostridial infection			
subjects affected / exposed	1 / 611 (0.16%)	1 / 343 (0.29%)	0 / 134 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Dermatitis infected			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Device related infection			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Eczema infected			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Empyema			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 611 (0.00%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Meningitis viral			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Nasal abscess			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Pertussis			

subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Pneumonia			
subjects affected / exposed	8 / 611 (1.31%)	2 / 343 (0.58%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 10	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Respiratory tract infection			
subjects affected / exposed	4 / 611 (0.65%)	0 / 343 (0.00%)	0 / 134 (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
Sepsis			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Urinary tract infection			

subjects affected / exposed	2 / 611 (0.33%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Dehydration			
subjects affected / exposed	3 / 611 (0.49%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Hypercalcaemia			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Hyponatraemia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 343 (0.00%)	0 / 134 (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
Oral intake reduced			

subjects affected / exposed	0 / 611 (0.00%)	1 / 343 (0.29%)	0 / 134 (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

Serious adverse events	BPC-NOLC: Placebo Only	BPC-OLC: Erlotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	41 / 132 (31.06%)	
number of deaths (all causes)	2	38	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Conjunctival neoplasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 11 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurilemmoma			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 11 (0.00%)	3 / 132 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer stage I			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma stage unspecified			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer stage unspecified			
subjects affected / exposed	0 / 11 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Throat cancer			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic occlusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterovaginal prolapse			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial fistula			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural fibrosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary granuloma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infarction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate affect			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 11 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial anastomosis complication			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polytraumatism			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rathke's cleft cyst			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain mass			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery embolism			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphasia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden onset of sleep			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness neurosensory			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric dysplasia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer perforation			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth resorption			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Calculus ureteric			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid cyst			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis acquired			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis acute			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis infected			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema infected			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal abscess			

subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 132 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral intake reduced			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	RC: Erlotinib	RC: Placebo	BPC-NOLC: Erlotinib/Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	590 / 611 (96.56%)	288 / 343 (83.97%)	125 / 134 (93.28%)
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 611 (3.60%)	14 / 343 (4.08%)	2 / 134 (1.49%)
occurrences (all)	27	17	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	37 / 611 (6.06%)	21 / 343 (6.12%)	6 / 134 (4.48%)
occurrences (all)	47	25	9
Chest pain			
subjects affected / exposed	15 / 611 (2.45%)	12 / 343 (3.50%)	2 / 134 (1.49%)
occurrences (all)	17	14	2
Fatigue			

subjects affected / exposed	118 / 611 (19.31%)	49 / 343 (14.29%)	23 / 134 (17.16%)
occurrences (all)	197	68	36
Mucosal inflammation			
subjects affected / exposed	27 / 611 (4.42%)	2 / 343 (0.58%)	6 / 134 (4.48%)
occurrences (all)	41	2	6
Non-cardiac chest pain			
subjects affected / exposed	12 / 611 (1.96%)	9 / 343 (2.62%)	1 / 134 (0.75%)
occurrences (all)	13	9	1
Oedema peripheral			
subjects affected / exposed	18 / 611 (2.95%)	11 / 343 (3.21%)	1 / 134 (0.75%)
occurrences (all)	24	13	1
Pyrexia			
subjects affected / exposed	23 / 611 (3.76%)	13 / 343 (3.79%)	6 / 134 (4.48%)
occurrences (all)	23	14	6
Xerosis			
subjects affected / exposed	19 / 611 (3.11%)	5 / 343 (1.46%)	0 / 134 (0.00%)
occurrences (all)	25	5	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	121 / 611 (19.80%)	69 / 343 (20.12%)	17 / 134 (12.69%)
occurrences (all)	153	86	18
Dyspnoea			
subjects affected / exposed	85 / 611 (13.91%)	61 / 343 (17.78%)	15 / 134 (11.19%)
occurrences (all)	103	78	20
Dyspnoea exertional			
subjects affected / exposed	9 / 611 (1.47%)	9 / 343 (2.62%)	2 / 134 (1.49%)
occurrences (all)	10	11	2
Epistaxis			
subjects affected / exposed	47 / 611 (7.69%)	4 / 343 (1.17%)	4 / 134 (2.99%)
occurrences (all)	59	6	5
Haemoptysis			
subjects affected / exposed	20 / 611 (3.27%)	4 / 343 (1.17%)	3 / 134 (2.24%)
occurrences (all)	24	4	4
Nasal ulcer			

subjects affected / exposed	5 / 611 (0.82%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences (all)	8	0	0
Pharyngolaryngeal pain			
subjects affected / exposed	13 / 611 (2.13%)	8 / 343 (2.33%)	3 / 134 (2.24%)
occurrences (all)	15	9	3
Pleural fibrosis			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	16 / 611 (2.62%)	14 / 343 (4.08%)	3 / 134 (2.24%)
occurrences (all)	21	16	4
Rhinorrhoea			
subjects affected / exposed	19 / 611 (3.11%)	12 / 343 (3.50%)	3 / 134 (2.24%)
occurrences (all)	22	14	3
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	20 / 611 (3.27%)	14 / 343 (4.08%)	5 / 134 (3.73%)
occurrences (all)	25	15	5
Depression			
subjects affected / exposed	33 / 611 (5.40%)	12 / 343 (3.50%)	5 / 134 (3.73%)
occurrences (all)	45	12	5
Insomnia			
subjects affected / exposed	40 / 611 (6.55%)	21 / 343 (6.12%)	6 / 134 (4.48%)
occurrences (all)	44	22	6
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 611 (1.15%)	6 / 343 (1.75%)	1 / 134 (0.75%)
occurrences (all)	15	8	1
Blood sodium decreased			
subjects affected / exposed	0 / 611 (0.00%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences (all)	0	0	0
Weight decreased			

subjects affected / exposed	56 / 611 (9.17%)	19 / 343 (5.54%)	2 / 134 (1.49%)
occurrences (all)	77	22	2
Weight increased			
subjects affected / exposed	16 / 611 (2.62%)	20 / 343 (5.83%)	1 / 134 (0.75%)
occurrences (all)	21	31	1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	9 / 611 (1.47%)	6 / 343 (1.75%)	4 / 134 (2.99%)
occurrences (all)	9	6	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	26 / 611 (4.26%)	22 / 343 (6.41%)	9 / 134 (6.72%)
occurrences (all)	31	25	9
Dysgeusia			
subjects affected / exposed	26 / 611 (4.26%)	4 / 343 (1.17%)	5 / 134 (3.73%)
occurrences (all)	32	5	6
Headache			
subjects affected / exposed	42 / 611 (6.87%)	40 / 343 (11.66%)	10 / 134 (7.46%)
occurrences (all)	49	45	12
Lethargy			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences (all)	2	0	0
Neuropathy			
subjects affected / exposed	9 / 611 (1.47%)	2 / 343 (0.58%)	1 / 134 (0.75%)
occurrences (all)	9	3	1
Paraesthesia			
subjects affected / exposed	20 / 611 (3.27%)	15 / 343 (4.37%)	1 / 134 (0.75%)
occurrences (all)	26	15	1
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 611 (1.47%)	4 / 343 (1.17%)	2 / 134 (1.49%)
occurrences (all)	19	4	2
Somnolence			
subjects affected / exposed	4 / 611 (0.65%)	0 / 343 (0.00%)	0 / 134 (0.00%)
occurrences (all)	4	0	0
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	16 / 611 (2.62%) 27	6 / 343 (1.75%) 12	2 / 134 (1.49%) 2
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	6 / 611 (0.98%) 6	6 / 343 (1.75%) 7	1 / 134 (0.75%) 1
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all) Eye irritation subjects affected / exposed occurrences (all)	34 / 611 (5.56%) 65 31 / 611 (5.07%) 41 8 / 611 (1.31%) 8	0 / 343 (0.00%) 0 3 / 343 (0.87%) 3 3 / 343 (0.87%) 3	1 / 134 (0.75%) 1 6 / 134 (4.48%) 9 2 / 134 (1.49%) 4
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Cheilitis subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dyspepsia	34 / 611 (5.56%) 44 28 / 611 (4.58%) 31 4 / 611 (0.65%) 4 35 / 611 (5.73%) 45 318 / 611 (52.05%) 639 21 / 611 (3.44%) 27	11 / 343 (3.21%) 15 20 / 343 (5.83%) 20 1 / 343 (0.29%) 1 23 / 343 (6.71%) 29 54 / 343 (15.74%) 86 3 / 343 (0.87%) 3	6 / 134 (4.48%) 7 0 / 134 (0.00%) 0 0 / 134 (0.00%) 0 7 / 134 (5.22%) 7 54 / 134 (40.30%) 78 7 / 134 (5.22%) 8

subjects affected / exposed	30 / 611 (4.91%)	14 / 343 (4.08%)	4 / 134 (2.99%)
occurrences (all)	34	15	6
Flatulence			
subjects affected / exposed	11 / 611 (1.80%)	6 / 343 (1.75%)	2 / 134 (1.49%)
occurrences (all)	11	9	2
Gastrooesophageal reflux disease			
subjects affected / exposed	20 / 611 (3.27%)	8 / 343 (2.33%)	1 / 134 (0.75%)
occurrences (all)	29	8	1
Mouth ulceration			
subjects affected / exposed	13 / 611 (2.13%)	1 / 343 (0.29%)	1 / 134 (0.75%)
occurrences (all)	14	1	1
Nausea			
subjects affected / exposed	84 / 611 (13.75%)	44 / 343 (12.83%)	17 / 134 (12.69%)
occurrences (all)	131	57	19
Stomatitis			
subjects affected / exposed	61 / 611 (9.98%)	4 / 343 (1.17%)	8 / 134 (5.97%)
occurrences (all)	78	4	9
Vomiting			
subjects affected / exposed	55 / 611 (9.00%)	23 / 343 (6.71%)	10 / 134 (7.46%)
occurrences (all)	69	25	12
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	25 / 611 (4.09%)	10 / 343 (2.92%)	6 / 134 (4.48%)
occurrences (all)	52	12	9
Alopecia			
subjects affected / exposed	67 / 611 (10.97%)	11 / 343 (3.21%)	12 / 134 (8.96%)
occurrences (all)	99	12	14
Blister			
subjects affected / exposed	8 / 611 (1.31%)	0 / 343 (0.00%)	5 / 134 (3.73%)
occurrences (all)	12	0	5
Dermatitis			
subjects affected / exposed	4 / 611 (0.65%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences (all)	5	1	0
Dermatitis acneiform			
subjects affected / exposed	111 / 611 (18.17%)	19 / 343 (5.54%)	37 / 134 (27.61%)
occurrences (all)	329	24	80

Dry skin			
subjects affected / exposed	127 / 611 (20.79%)	50 / 343 (14.58%)	15 / 134 (11.19%)
occurrences (all)	218	90	20
Eczema			
subjects affected / exposed	11 / 611 (1.80%)	5 / 343 (1.46%)	0 / 134 (0.00%)
occurrences (all)	20	6	0
Erythema			
subjects affected / exposed	24 / 611 (3.93%)	5 / 343 (1.46%)	10 / 134 (7.46%)
occurrences (all)	34	8	16
Exfoliative rash			
subjects affected / exposed	19 / 611 (3.11%)	2 / 343 (0.58%)	2 / 134 (1.49%)
occurrences (all)	35	4	2
Nail disorder			
subjects affected / exposed	23 / 611 (3.76%)	2 / 343 (0.58%)	1 / 134 (0.75%)
occurrences (all)	53	3	2
Night sweats			
subjects affected / exposed	3 / 611 (0.49%)	0 / 343 (0.00%)	4 / 134 (2.99%)
occurrences (all)	3	0	4
Pruritus			
subjects affected / exposed	161 / 611 (26.35%)	51 / 343 (14.87%)	21 / 134 (15.67%)
occurrences (all)	247	73	26
Rash			
subjects affected / exposed	356 / 611 (58.27%)	58 / 343 (16.91%)	51 / 134 (38.06%)
occurrences (all)	895	74	102
Rash erythematous			
subjects affected / exposed	30 / 611 (4.91%)	6 / 343 (1.75%)	6 / 134 (4.48%)
occurrences (all)	57	10	9
Rash macular			
subjects affected / exposed	18 / 611 (2.95%)	7 / 343 (2.04%)	2 / 134 (1.49%)
occurrences (all)	36	12	6
Rash maculo-papular			
subjects affected / exposed	28 / 611 (4.58%)	3 / 343 (0.87%)	4 / 134 (2.99%)
occurrences (all)	84	3	15
Rash papular			
subjects affected / exposed	25 / 611 (4.09%)	5 / 343 (1.46%)	1 / 134 (0.75%)
occurrences (all)	44	6	1

Rash pruritic subjects affected / exposed occurrences (all)	10 / 611 (1.64%) 17	1 / 343 (0.29%) 1	1 / 134 (0.75%) 1
Skin exfoliation subjects affected / exposed occurrences (all)	23 / 611 (3.76%) 35	4 / 343 (1.17%) 4	6 / 134 (4.48%) 6
Skin fissures subjects affected / exposed occurrences (all)	26 / 611 (4.26%) 44	2 / 343 (0.58%) 18	1 / 134 (0.75%) 1
Skin lesion subjects affected / exposed occurrences (all)	15 / 611 (2.45%) 20	4 / 343 (1.17%) 4	1 / 134 (0.75%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	23 / 611 (3.76%) 28	25 / 343 (7.29%) 29	4 / 134 (2.99%) 4
Back pain subjects affected / exposed occurrences (all)	40 / 611 (6.55%) 45	24 / 343 (7.00%) 30	3 / 134 (2.24%) 3
Muscle spasms subjects affected / exposed occurrences (all)	36 / 611 (5.89%) 56	7 / 343 (2.04%) 9	1 / 134 (0.75%) 1
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	28 / 611 (4.58%) 37	10 / 343 (2.92%) 13	1 / 134 (0.75%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	20 / 611 (3.27%) 23	23 / 343 (6.71%) 27	2 / 134 (1.49%) 2
Myalgia subjects affected / exposed occurrences (all)	18 / 611 (2.95%) 21	6 / 343 (1.75%) 6	4 / 134 (2.99%) 4
Pain in extremity subjects affected / exposed occurrences (all)	23 / 611 (3.76%) 27	12 / 343 (3.50%) 18	3 / 134 (2.24%) 5
Infections and infestations			

Bronchitis			
subjects affected / exposed	21 / 611 (3.44%)	12 / 343 (3.50%)	1 / 134 (0.75%)
occurrences (all)	28	14	1
Ear infection			
subjects affected / exposed	2 / 611 (0.33%)	1 / 343 (0.29%)	0 / 134 (0.00%)
occurrences (all)	2	3	0
Localised infection			
subjects affected / exposed	4 / 611 (0.65%)	2 / 343 (0.58%)	0 / 134 (0.00%)
occurrences (all)	4	3	0
Nail infection			
subjects affected / exposed	2 / 611 (0.33%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences (all)	2	0	2
Nasopharyngitis			
subjects affected / exposed	29 / 611 (4.75%)	30 / 343 (8.75%)	2 / 134 (1.49%)
occurrences (all)	39	46	2
Paronychia			
subjects affected / exposed	39 / 611 (6.38%)	2 / 343 (0.58%)	4 / 134 (2.99%)
occurrences (all)	74	2	6
Pneumonia			
subjects affected / exposed	16 / 611 (2.62%)	5 / 343 (1.46%)	1 / 134 (0.75%)
occurrences (all)	17	5	2
Rash pustular			
subjects affected / exposed	19 / 611 (3.11%)	1 / 343 (0.29%)	3 / 134 (2.24%)
occurrences (all)	49	1	6
Rhinitis			
subjects affected / exposed	12 / 611 (1.96%)	6 / 343 (1.75%)	1 / 134 (0.75%)
occurrences (all)	14	6	3
Sinusitis			
subjects affected / exposed	7 / 611 (1.15%)	8 / 343 (2.33%)	3 / 134 (2.24%)
occurrences (all)	7	8	3
Skin infection			
subjects affected / exposed	3 / 611 (0.49%)	0 / 343 (0.00%)	1 / 134 (0.75%)
occurrences (all)	3	0	3
Upper respiratory tract infection			
subjects affected / exposed	30 / 611 (4.91%)	15 / 343 (4.37%)	0 / 134 (0.00%)
occurrences (all)	40	17	0

Urinary tract infection subjects affected / exposed occurrences (all)	19 / 611 (3.11%) 24	12 / 343 (3.50%) 17	1 / 134 (0.75%) 1
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	80 / 611 (13.09%) 97	24 / 343 (7.00%) 38	20 / 134 (14.93%) 23
Dehydration subjects affected / exposed occurrences (all)	5 / 611 (0.82%) 5	1 / 343 (0.29%) 1	4 / 134 (2.99%) 4

Non-serious adverse events	BPC-NOLC: Placebo Only	BPC-OLC: Erlotinib	
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 11 (36.36%)	130 / 132 (98.48%)	
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	8 / 132 (6.06%) 21	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	6 / 132 (4.55%) 7	
Chest pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 132 (3.03%) 5	
Fatigue subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	34 / 132 (25.76%) 71	
Mucosal inflammation subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	12 / 132 (9.09%) 12	
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 132 (3.03%) 4	
Oedema peripheral			

subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	7	
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)	9 / 132 (6.82%)	
occurrences (all)	1	12	
Xerosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 11 (0.00%)	29 / 132 (21.97%)	
occurrences (all)	0	42	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	18 / 132 (13.64%)	
occurrences (all)	0	22	
Dyspnoea exertional			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	11 / 132 (8.33%)	
occurrences (all)	0	15	
Haemoptysis			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Nasal ulcer			
subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	8	
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	5	
Pleural fibrosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Productive cough			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	6 / 132 (4.55%) 7	
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	7 / 132 (5.30%) 7	
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 132 (0.00%) 0	
Anxiety subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	7 / 132 (5.30%) 8	
Depression subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	6 / 132 (4.55%) 6	
Insomnia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	16 / 132 (12.12%) 20	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 132 (3.03%) 4	
Blood sodium decreased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 132 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	19 / 132 (14.39%) 28	
Weight increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	6 / 132 (4.55%) 6	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	5 / 132 (3.79%) 5	
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	13 / 132 (9.85%)	
occurrences (all)	1	16	
Dysgeusia			
subjects affected / exposed	0 / 11 (0.00%)	13 / 132 (9.85%)	
occurrences (all)	0	17	
Headache			
subjects affected / exposed	0 / 11 (0.00%)	13 / 132 (9.85%)	
occurrences (all)	0	16	
Lethargy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Neuropathy			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	10	
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 132 (0.00%)	
occurrences (all)	0	0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	5	
Somnolence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	5	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	5	
Dry eye			

subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	5	
Eye irritation			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	14 / 132 (10.61%)	
occurrences (all)	0	27	
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	11 / 132 (8.33%)	
occurrences (all)	0	14	
Cheilitis			
subjects affected / exposed	0 / 11 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	10	
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	14 / 132 (10.61%)	
occurrences (all)	0	15	
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	86 / 132 (65.15%)	
occurrences (all)	0	199	
Dry mouth			
subjects affected / exposed	0 / 11 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	10	
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	15 / 132 (11.36%)	
occurrences (all)	0	17	
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Mouth ulceration			
subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	10	

Nausea			
subjects affected / exposed	1 / 11 (9.09%)	28 / 132 (21.21%)	
occurrences (all)	1	41	
Stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	15 / 132 (11.36%)	
occurrences (all)	0	18	
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)	12 / 132 (9.09%)	
occurrences (all)	0	19	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 11 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	22 / 132 (16.67%)	
occurrences (all)	0	27	
Blister			
subjects affected / exposed	0 / 11 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	4	
Dermatitis			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Dermatitis acneiform			
subjects affected / exposed	0 / 11 (0.00%)	45 / 132 (34.09%)	
occurrences (all)	0	159	
Dry skin			
subjects affected / exposed	0 / 11 (0.00%)	41 / 132 (31.06%)	
occurrences (all)	0	91	
Eczema			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Erythema			
subjects affected / exposed	0 / 11 (0.00%)	13 / 132 (9.85%)	
occurrences (all)	0	15	
Exfoliative rash			

subjects affected / exposed	0 / 11 (0.00%)	11 / 132 (8.33%)
occurrences (all)	0	21
Nail disorder		
subjects affected / exposed	0 / 11 (0.00%)	9 / 132 (6.82%)
occurrences (all)	0	11
Night sweats		
subjects affected / exposed	1 / 11 (9.09%)	1 / 132 (0.76%)
occurrences (all)	1	1
Pruritus		
subjects affected / exposed	0 / 11 (0.00%)	29 / 132 (21.97%)
occurrences (all)	0	54
Rash		
subjects affected / exposed	0 / 11 (0.00%)	72 / 132 (54.55%)
occurrences (all)	0	219
Rash erythematous		
subjects affected / exposed	0 / 11 (0.00%)	12 / 132 (9.09%)
occurrences (all)	0	20
Rash macular		
subjects affected / exposed	0 / 11 (0.00%)	8 / 132 (6.06%)
occurrences (all)	0	12
Rash maculo-papular		
subjects affected / exposed	0 / 11 (0.00%)	7 / 132 (5.30%)
occurrences (all)	0	9
Rash papular		
subjects affected / exposed	0 / 11 (0.00%)	7 / 132 (5.30%)
occurrences (all)	0	16
Rash pruritic		
subjects affected / exposed	1 / 11 (9.09%)	5 / 132 (3.79%)
occurrences (all)	1	8
Skin exfoliation		
subjects affected / exposed	0 / 11 (0.00%)	8 / 132 (6.06%)
occurrences (all)	0	12
Skin fissures		
subjects affected / exposed	0 / 11 (0.00%)	9 / 132 (6.82%)
occurrences (all)	0	11
Skin lesion		

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 132 (3.03%) 4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	14 / 132 (10.61%)	
occurrences (all)	0	18	
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	12 / 132 (9.09%)	
occurrences (all)	0	14	
Muscle spasms			
subjects affected / exposed	0 / 11 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	12	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Musculoskeletal pain			
subjects affected / exposed	0 / 11 (0.00%)	9 / 132 (6.82%)	
occurrences (all)	0	12	
Myalgia			
subjects affected / exposed	0 / 11 (0.00%)	6 / 132 (4.55%)	
occurrences (all)	0	9	
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	12 / 132 (9.09%)	
occurrences (all)	0	21	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	9 / 132 (6.82%)	
occurrences (all)	0	13	
Ear infection			
subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	7	
Localised infection			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Nail infection			

subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	5	
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	17 / 132 (12.88%)	
occurrences (all)	0	25	
Paronychia			
subjects affected / exposed	0 / 11 (0.00%)	6 / 132 (4.55%)	
occurrences (all)	0	11	
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Rash pustular			
subjects affected / exposed	0 / 11 (0.00%)	13 / 132 (9.85%)	
occurrences (all)	0	18	
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	8	
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	10	
Skin infection			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	13 / 132 (9.85%)	
occurrences (all)	0	18	
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 11 (9.09%)	20 / 132 (15.15%)	
occurrences (all)	1	27	
Dehydration			
subjects affected / exposed	0 / 11 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2007	<ol style="list-style-type: none">1. Added a section describing the breach in GCP relating to the IVRS error and the options offered patients to remain in the study with or without receiving open-label erlotinib, or withdraw consent from treatment and assessments.2. Clarified that the approximately 1730 patients to be screened would not include the 278 patients enrolled prior to 07 November 2007 who were part of the BPC. Note that 1 patient in the BPC was randomized and received study drug but did not have HIPAA documentation at the site; therefore, the data for this patient was removed from the database resulting in a total of 277 patients in the BPC.3. Added an appendix to present the procedures to be followed for patients in the BPC, including schedules of on-treatment, posttreatment and long-term follow-up assessments. References to this appendix were added throughout the protocol, as appropriate.4. Updated the inclusion criterion to require nodal dissection of 2 separate mediastinal nodal stations or nodal sampling of 2 separate mediastinal nodal stations. Added an appendix to clarify this inclusion criterion.5. Added patient contact as an on-treatment assessment for the evaluation of skin reactions approximately 8 to 14 days after receipt of study drug.6. Re-iterated in the statistical methods that the planned sample sized applied only to patients randomized after 07 November 2007.7. Included other minor clarifications in the protocol text.
13 December 2010	<ol style="list-style-type: none">1. Updated the study rationale to describe the findings from the SATURN study.2. Revised the primary objectives to remove the assessment of DFS in a subset population.3. Added secondary objectives to compare DFS and OS in patients with EGFR mutation-positive tumors.4. Revised the end of the study to approximately 6 months after the date when at least 403 deaths have occurred among patients participating in the study.5. Clarified that long-term follow-up should continue at least yearly or until death or until both the primary DFS objective and the secondary OS objective of the study had been satisfied.6. Updated the description of the objectives in the statistical methods section to align with the revised study objectives and to remove reference to more than 1 interim analysis.7. Revised the description of the sample size calculation to reflect the new objectives and the change in the determination of the end of the study. Reference to more than 1 interim analysis was also removed.8. Revised the statistical methods for efficacy to reflect the change in the objectives.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 November 2007	On 07 November 2007, the study sponsor became aware of an error in the drug dispensing module of the IVRS that resulted in most of the 278 patients randomized prior to that date being assigned an incorrect bottle at least once, and often multiple times, during their participation in the study. Procedures relating to this cohort were presented in Amendment 1.	21 November 2007

Notes:

Limitations and caveats

None reported