Clinical trial results:
A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination with Ramucirumab or Placebo in Previously Untreated Patients with EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

Summary

EudraCT number	2014-004824-22
Trial protocol	ES DE FR GR IT
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	04 April 2020
First version publication date	02 February 2020
Version creation reason	• Correction of full data set Corrections for alignment with results.

Trial information

Trial identification

Sponsor protocol code	I4T-MC-JVCY

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02411448
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15540

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	23 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy and safety of ramucirumab in combination with erlotinib as compared to placebo in combination with erlotinib in previously untreated participants with stage IV non-small cell lung cancer (NSCLC) harboring an activating epidermal growth factor receptor (EGFR) mutation (Exon 19-Del and Exon 21 L858R). Safety and tolerability of ramucirumab in combination with erlotinib will be assessed in Part A before proceeding to Part B.
The purpose of Part C is to determine the efficacy and safety of ramucirumab in combination with gefitinib in previously untreated East Asian participants with EGFR mutation-positive metastatic NSCLC and of ramucirumab in combination with osimertinib in those participants whose disease progressed on ramucirumab and gefitinib and that have T790M - positive metastatic NSCLC.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	21 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Korea, Republic of: 54
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Taiwan: 56
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Japan: 218

Worldwide total number of subjects	463
EEA total number of subjects	102

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)	220
From 65 to 84 years	241
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

This study consists of 3 parts:
- Part A: open-label.
- Part B: randomized, double-blind and placebo-controlled.
- Part C: Open-label.

Part C data will be reported after study completion.

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, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Ramucirumab + Erlotinib

Arm description:

Part A: 10 milligrams per kilogram (mg/kg) ramucirumab administered every 2 weeks intravenously (IV) in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	LY3009806
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 milligrams per kilogram (mg/kg) ramucirumab administered every 2 weeks intravenously (IV).

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

Dosage and administration details:

150 mg erlotinib daily orally.

Arm title	Part B: Ramucirumab+ Erlotinib

Arm description:

Part B: 10 mg/kg ramucirumab administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Arm type	Placebo

Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	LY3009806
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 milligrams per kilogram (mg/kg) ramucirumab administered every 2 weeks intravenously (IV).

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

Dosage and administration details:

150 mg erlotinib daily orally.

Arm title	Part B: Placebo+ Erlotinib

Arm description:

Part B: Placebo administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo administered every 2 weeks.

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

Dosage and administration details:

150 mg erlotinib daily orally.

Number of subjects in period 1	Part A: Ramucirumab + Erlotinib	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib
Started	14	224	225
Received at least one dose of study drug	14	221	225
Completed	10	141	173
Not completed	4	83	52
Consent withdrawn by subject	1	14	9
Not Specified	-	2	-
Alive on study treatment	3	64	43
Did not receive study treatment	-	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Ramucirumab + Erlotinib
Reporting group description:	
Part A: 10 milligrams per kilogram (mg/kg) ramucirumab administered every 2 weeks intravenously (IV) in combination with 150 mg erlotinib daily orally. Participants may continue to receive treatment until discontinuation criteria are met.	
Reporting group title	Part B: Ramucirumab+ Erlotinib
Reporting group description:	
Part B: 10 mg/kg ramucirumab administered every 2 weeks IV in combination with 150 mg erlotinib daily orally. Participants may continue to receive treatment until discontinuation criteria are met.	
Reporting group title	Part B: Placebo+ Erlotinib
Reporting group description:	
Part B: Placebo administered every 2 weeks IV in combination with 150 mg erlotinib daily orally. Participants may continue to receive treatment until discontinuation criteria are met.	

Reporting group values	Part A: Ramucirumab + Erlotinib	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib
Number of subjects	14	224	225
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	67.6	63.7	62.9
standard deviation	± 13.2	± 10.2	± 10.6
Gender categorical Units: Subjects			
Female	11	141	142
Male	3	83	83
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	13	10
Not Hispanic or Latino	1	150	160
Unknown or Not Reported	13	61	55
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	7	172	174
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	7	52	48
More than one race	0	0	0
Unknown or Not Reported	0	0	1
Region of Enrollment			

Units: Subjects			
Romania	0	2	0
Hong Kong	0	9	6
United States	0	7	2
Japan	7	106	105
United Kingdom	0	4	3
Spain	7	23	19
Canada	0	0	2
South Korea	0	25	29
Turkey	0	3	4
Taiwan	0	26	30
Italy	0	8	12
France	0	4	7
Germany	0	7	6
Geographic Region			
* Geographic region "Other" includes Canada, France, Germany, Italy, Romania, Spain, Turkey, US, UK.			
Units: Subjects			
East Asia	7	166	170
Other*	7	58	55

Reporting group values	Total		
Number of subjects	463		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	294		
Male	169		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	23		
Not Hispanic or Latino	311		
Unknown or Not Reported	129		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	353		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	107		
More than one race	0		
Unknown or Not Reported	1		
Region of Enrollment Units: Subjects			
Romania	2		

Hong Kong	15		
United States	9		
Japan	218		
United Kingdom	7		
Spain	49		
Canada	2		
South Korea	54		
Turkey	7		
Taiwan	56		
Italy	20		
France	11		
Germany	13		
Geographic Region			
* Geographic region “Other” includes Canada, France, Germany, Italy, Romania, Spain, Turkey, US, UK.			
Units: Subjects			
East Asia	343		
Other*	120		

End points

End points reporting groups

Reporting group title	Part A: Ramucirumab + Erlotinib

Reporting group description:

Part A: 10 milligrams per kilogram (mg/kg) ramucirumab administered every 2 weeks intravenously (IV) in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Reporting group title	Part B: Ramucirumab+ Erlotinib

Reporting group description:

Part B: 10 mg/kg ramucirumab administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Reporting group title	Part B: Placebo+ Erlotinib

Reporting group description:

Part B: Placebo administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Subject analysis set title	Part B: Ramucirumab + Erlotinib
Subject analysis set type	Per protocol

Subject analysis set description:

Part B: 10 mg/kg ramucirumab administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Subject analysis set title	Part B: Placebo + Erlotinib
Subject analysis set type	Per protocol

Subject analysis set description:

Part B: Placebo administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Primary: Part B: Progression Free Survival (PFS)

End point title	Part B: Progression Free Survival (PFS)[1]

End point description:

PFS is defined as the time from the date of randomization to the date of radiographically documented progressive disease (PD) based on investigator assessment, or the date of death due to any cause, whichever is first assessed via Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

Analysis Population Description (APD): Part B: All randomized participants grouped according to their assigned treatment at randomization. Censored participants were: Part B: Ramucirumab+ Erlotinib= 102 and Part B: Placebo+ Erlotinib= 67. Per protocol, Part A did not evaluate efficacy.

End point type	Primary

End point timeframe:

Randomization to Measured Progressive Disease or Death from Any Cause (Up To 37 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: Per protocol, there were no statistical analysis planned for this outcome measure.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	225		
Units: Months				
median (confidence interval 95%)	19.4 (15.4 to 21.6)	12.4 (11.0 to 13.5)		

Statistical analyses

Statistical analysis title	Part B: Progression Free Survival (PFS)
Comparison groups	Part B: Placebo+ Erlotinib v Part B: Ramucirumab+ Erlotinib
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.591
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.461
upper limit	0.76

Primary: Number of Participants with Treatment-Emergent Adverse Events

End point title	Number of Participants with Treatment-Emergent Adverse Events[2]

End point description:

A summary of other non-serious adverse events and all serious adverse events, regardless of causality, is located in the Reported Adverse Events Section.

Analysis Population Description: All randomized participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Cycle 1 Day 1 through End of Study (Up To 3 Years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, there were no statistical analysis planned for this outcome measure.

End point values	Part A: Ramucirumab + Erlotinib	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	221	225	
Units: participants	14	221	225	

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Overall Survival (OS)

End point title	Part B: Overall Survival (OS)[3]

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. For each participant who was not known to have died as of the data-inclusion cutoff date for a particular analysis, OS was censored for that analysis at the date of last contact prior to the data-inclusion cutoff date (contacts considered in the determination of last contact date include adverse event (AE) date, lesion assessment date, visit date, and last known alive date).

Analysis Population Description: Part B: All randomized participants grouped according to their assigned treatment at randomization. Censored participants were: Part B: Ramucirumab+ Erlotinib= 187 and Part B: Placebo+ Erlotinib= 183. Per protocol, Part A did not evaluate efficacy.

End point type	Secondary

End point timeframe:

Randomization to Date of Death from Any Cause (Up To 37 Months)

9999=NA.
Interim OS data were immature due to high censoring.

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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224[4]	225[5]		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[4] - 9999=NA.
There were not enough events/deaths to compute a median or 95% confidence interval.
[5] - 9999=NA.
There were not enough events/deaths to compute a median or 95% confidence interval.

Statistical analyses

Statistical analysis title	Part B: Overall Survival (OS)
Comparison groups	Part B: Ramucirumab+ Erlotinib v Part B: Placebo+ Erlotinib

Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4209
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.832
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.532
upper limit	1.303

Secondary: Part B: Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Objective Response Rate [ORR])

End point title	Part B: Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Objective Response Rate [ORR])[6]

End point description:

ORR was defined as the percentage of randomized participants achieving a best overall response of partial response (PR) or complete response (CR) assessed via Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. CR was defined as the disappearance of all lesions, pathological lymph node reduction in short axis to <10 mm, and normalization of tumor marker levels of non-target lesions. PR was at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

Randomization to Disease Progression (Up To 37 Months)

Analysis Population Description: Part B: All randomized participants grouped according to their assigned treatment at randomization. Per protocol, Part A did not evaluate efficacy.

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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	225		
Units: percentage of participants				
number (confidence interval 95%)	76.3 (70.8 to 81.9)	74.7 (69.0 to 80.3)		

Statistical analyses

Statistical analysis title	Part B: Percentage of Participants With ORR
Comparison groups	Part B: Ramucirumab+ Erlotinib v Part B: Placebo+ Erlotinib
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7413
Method	Cochran-Mantel-Haenszel

Secondary: Part B: Percentage of Participants With CR, PR, or Stable Disease (SD) (Disease Control Rate [DCR])

End point title	Part B: Percentage of Participants With CR, PR, or Stable Disease (SD) (Disease Control Rate [DCR])[7]

End point description:

DCR was defined as the percentage of randomized participants achieving a best overall response of CR,PR, or stable disease(SD) assessed via Response Evaluation Criteria in Solid Tumors(RECIST) version 1.1. CR was defined as the disappearance of all lesions,pathological lymph node reduction in short axis to <10 mm, and normalization of tumor marker levels of non-target lesions.PR was at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Progressive Disease(PD) was at least a 20% increase in the sum of the diameters of target lesions,taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.The appearance of 1 or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

Randomization to Disease Progression (Up To 37 Months)

Analysis Population Description: Part B: All randomized participants grouped according to their assigned treatment at randomization. Per protocol, Part A did not evaluate efficacy.

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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	225		
Units: percentage of participants				
number (confidence interval 95%)	95.1 (92.3 to 97.9)	95.6 (92.9 to 98.2)		

Statistical analyses

Statistical analysis title	Part B: Percentage of Participants With DCR
Comparison groups	Part B: Ramucirumab+ Erlotinib v Part B: Placebo+ Erlotinib

Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Cochran-Mantel-Haenszel

Secondary: Part B: Duration of Response (DoR)

End point title	Part B: Duration of Response (DoR)[8]

End point description:

DoR was defined as the date of first documented CR or PR (responder) to the date of objective progression or the date of death due to any cause, whichever was earlier. If a responder was not known to have died or have objective progression, then the patient was censored at the date of last evaluable tumor assessment.CR was defined as the disappearance of all lesions, pathological lymph node reduction in short axis to <10 mm, and normalization of tumor marker levels of non-target lesions. PR was at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

Date of CR or PR to Date of Objective Disease Progression or Death Due to Any Cause (Up To 37 Months)

APD: Part B: All randomized participants grouped according to their assigned treatment at randomization that had a response (CR or PR).

Notes:

[8] - 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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	168		
Units: months				
median (confidence interval 95%)	18.0 (13.9 to 19.8)	11.1 (9.7 to 12.3)		

Statistical analyses

Statistical analysis title	Part B: Duration of Response (DoR)
Comparison groups	Part B: Ramucirumab+ Erlotinib v Part B: Placebo+ Erlotinib
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.619

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	0.805

Secondary: Part B: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab

End point title	Part B: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab[9]

End point description:

Part B: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab

Analysis Population Description: Part B participants who received at least one dose of Ramucirumab+ Erlotinib who had evaluable PK data. Per protocol, Part A did not evaluate PK.

Geometric coefficient of variation is in percentage.

End point type	Secondary

End point timeframe:

Cycle 2 Day 1: Predose; Cycle 4 Day 1: Predose; Cycle 7 Day 1: Predose; Cycle 14 Day 1

Notes:

[9] - 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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	185			
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 2	39.6 (± 32)			
Cycle 4	68.5 (± 37)			
Cycle 7	85.7 (± 32)			
Cycle 14	99.4 (± 31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Participants with Anti-Ramucirumab Antibodies

End point title	Part B: Number of Participants with Anti-Ramucirumab Antibodies[10]

End point description:

Part B: Number of Participants With Anti-Ramucirumab Antibodies.

Analysis Population Description: All participants who received at least one dose of study drug. Per protocol, Part A did not evaluate Anti-Ramucirumab Antibodies.

End point type	Secondary

End point timeframe:

Cycle 1 Predose through Follow-up (Up To 37 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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	225		
Units: participants	14	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Best Change from Baseline on the Lung Cancer Symptom Scale (LCSS)

End point title	Part B: Best Change from Baseline on the Lung Cancer Symptom Scale (LCSS)[11]

End point description:

The LCSS consisted of 9 items: 6 items focused on lung cancer symptoms [loss of appetite, fatigue, cough, dyspnea (shortness of breath), hemoptysis (blood in sputum), and pain] and 3 global items (symptom distress, interference with activity level, and global quality of life). Participant responses to each item were measured using visual analogue scales (VAS) with 100-millimeter (mm) lines. A higher score for any item represented a higher level of symptoms/problems. The LCSS total score was defined as the mean of all 9 items. Average symptom burden index (ASBI) was calculated as the mean of the six symptom-specific questions from the LCSS. Potential scores range from 0 (for best outcome) to 100 (for worst outcome).

End point type	Secondary

End point timeframe:

Baseline, End of Study (Up To 37 Months)

Analysis Population Description: Part B:All randomized participants who completed the LCSS at baseline and at least once post-baseline. Per protocol, Part A did not evaluate efficacy.

Notes:

[11] - 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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217[12]		
Units: millimeter				
least squares mean (standard error)				
Appetite	-17.07 (± 0.92)	-18.16 (± 0.91)		
Fatigue	-19.35 (± 0.91)	-19.45 (± 0.90)		

Shortness of Breath	-14.46 (± 0.57)	-15.93 (± 0.57)		
Blood in Sputum	-1.58 (± 0.25)	-1.94 (± 0.25)		
Pain	-13.57 (± 0.59)	-14.69 (± 0.59)		
Average Symptom Burden Index	-12.17 (± 0.57)	-13.05 (± 0.57)		
Total LCSS	-12.00 (± 0.62)	-12.71 (± 0.61)		
Cough	-21.22 (± 0.58)	-22.09 (± 0.57)		
Interference with Activity Level	-14.43 (± 0.83)	-15.60 (± 0.82)		
Symptom distress	-15.91 (± 0.67)	-16.15 (± 0.67)		
Global Quality of Life	-16.21 (± 0.95)	-18.12 (± 0.94)		

Notes:

[12] - The N for Blood in Sputum, pain, Average Symptom Burden Index and Total LCSS is 216.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change from Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score

End point title	Part B: Change from Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score[13]

End point description:

The EQ-5D-5L is a standardized instrument used to measure self-reported health status of the patient. It consists of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). There are 5 response levels (no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to), ranging from 1 to 5 (good to bad). Dimension responses were converted to an index score using UK weights. The index scores were anchored on full health (1.0) to dead (0) with negative values assigned to health states considered worse than death.

Analysis Population Description: Part B: All randomized participants who completed the EQ-5D-5L at baseline and at least once post-baseline. Per protocol, Part A did not evaluate efficacy.

End point type	Secondary

End point timeframe:

Baseline, Cycle 10 (each cycle is 2 weeks)

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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: score on a scale				
arithmetic mean (standard deviation)	0.02 (± 0.15)	0.02 (± 0.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change from Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score

End point title	Part B: Change from Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score[14]

End point description:

The EQ-5D-5L is a standardized instrument used to measure self-reported health status of the participants. It consists of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). There are 5 response levels (no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to), ranging from 1 to 5 (good to bad). Dimension responses were converted to an index score using UK weights. The index scores were anchored on full health (1.0) to dead (0) with negative values assigned to health states considered worse than death.

End point type	Secondary

End point timeframe:

Baseline, Cycle 28 (each cycle is 2 weeks)

Analysis Population Description: Part B: All randomized participants who completed the EQ-5D-5L at baseline and at least once post-baseline. Per protocol, Part A did not evaluate efficacy.

Notes:

[14] - 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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	81		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.02 (± 0.18)	0.01 (± 0.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score

End point title	Part B: Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score[15]

End point description:

The EQ-5D-5L is a standardized instrument used to measure self-reported health status of the participants. It consists of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). There are 5 response levels (no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to), ranging from 1 to 5 (good to bad). Dimension responses were converted to an index score using UK weights. The index scores were anchored on full health (1.0) to dead (0) with negative values assigned to health states considered worse than death.

End point type	Secondary

End point timeframe:

Baseline, Cycle 40 (each cycle is 2 weeks)

Analysis Population Description: Part B: All randomized participants who completed the EQ-5D-5L at baseline and at least once post-baseline. Per protocol, Part A did not evaluate efficacy.

Notes:

[15] - 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: Per protocol, Part A did not evaluate efficacy.

End point values	Part B: Ramucirumab+ Erlotinib	Part B: Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	44		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.01 (± 0.15)	-0.01 (± 0.14)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up To 3 Years

Adverse event reporting additional description:

Serious Adverse Events and Other Adverse Events: All participants who received at least one dose of study drug; All-Cause Mortality: All randomized participants. Part C data will be reported after study completion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Part A: Ramucirumab+Erlotinib

Reporting group description:

Part A: 10 milligrams per kilogram (mg/kg) ramucirumab administered every 2 weeks intravenously (IV) in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Reporting group title	Part B: Ramucirumab+Erlotinib

Reporting group description:

Part B: 10 mg/kg ramucirumab administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Reporting group title	Part B: Placebo+Erlotinib

Reporting group description:

Part B: Placebo administered every 2 weeks IV in combination with 150 mg erlotinib daily orally.

Participants may continue to receive treatment until discontinuation criteria are met.

Serious adverse events	Part A: Ramucirumab+Erlotinib	Part B: Ramucirumab+Erlotinib	Part B: Placebo+Erlotinib
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	65 / 221 (29.41%)	47 / 225 (20.89%)
number of deaths (all causes)	0	6	1
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
adenocarcinoma of colon			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
basal cell carcinoma			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cancer pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lymphoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
mesenteric neoplasm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
ovarian neoplasm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[1]	0 / 11 (0.00%)	1 / 139 (0.72%)	0 / 142 (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
pericarditis malignant			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
embolism			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypotension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	0 / 225 (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
Surgical and medical procedures			
hepatectomy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
fatigue			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
general physical health deterioration			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
malaise			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
mucous membrane disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
non-cardiac chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyrexia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	3 / 221 (1.36%)	4 / 225 (1.78%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
endometriosis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed[2]	0 / 11 (0.00%)	0 / 139 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
dysphonia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
dyspnoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dyspnoea exertional			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemoptysis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemothorax			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
interstitial lung disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
pleural effusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
pleurisy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
pneumomediastinum			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
pneumonitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
pneumothorax			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	4 / 221 (1.81%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	0 / 0	1 / 5	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

pulmonary embolism			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
adjustment disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood creatinine increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
concussion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

fall			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
humerus fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infusion related reaction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
radius fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
rib fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
ulna fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
cardiac failure			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
cardiac failure congestive			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
myocardial infarction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
pericardial effusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
wolff-parkinson-white syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
depressed level of consciousness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dizziness			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
hydrocephalus			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
neuralgia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
somnolence			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
transient ischaemic attack			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
Eye disorders			
cataract			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
macular fibrosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
retinal detachment			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
abdominal pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
colitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
colitis ischaemic			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
constipation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	3 / 221 (1.36%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
duodenal ulcer			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dyspepsia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemorrhoids			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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

irritable bowel syndrome			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
melaena			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
small intestinal haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	0 / 225 (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
stomatitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
drug-induced liver injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatic function abnormal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	3 / 221 (1.36%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	3 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatic steatosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
liver disorder			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
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 and subcutaneous tissue disorders			
dermatitis acneiform			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
dermatitis exfoliative generalised			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
eczema asteatotic			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
skin exfoliation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
proteinuria			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
renal failure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
back pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neck pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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			
abdominal infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
appendicitis perforated			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cellulitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	4 / 221 (1.81%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diverticulitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
empyema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
encephalitis influenzal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
gastroenteritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
gastroenteritis bacterial			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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

herpes zoster			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
infectious pleural effusion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
meningitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
pneumonia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	7 / 221 (3.17%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
pneumonia bacterial			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
rash pustular			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sepsis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
septic shock			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
skin infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	0 / 225 (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
tonsillitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper respiratory tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 221 (0.90%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	3 / 221 (1.36%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 0	6 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyperglycaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
hypokalaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	0 / 225 (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
hyponatraemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

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

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

Non-serious adverse events	Part A: Ramucirumab+Erlotinib	Part B: Ramucirumab+Erlotinib	Part B: Placebo+Erlotinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	220 / 221 (99.55%)	225 / 225 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

cancer pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	4 / 225 (1.78%)
occurrences (all)	1	1	5
pyogenic granuloma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	4 / 221 (1.81%)	0 / 225 (0.00%)
occurrences (all)	2	6	0
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	7 / 14 (50.00%)	100 / 221 (45.25%)	27 / 225 (12.00%)
occurrences (all)	27	246	72
thrombosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
varicose ulceration			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
dental care			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
dental operation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
inguinal hernia repair			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
tooth extraction			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	3 / 225 (1.33%)
occurrences (all)	1	3	3
vaginal pessary insertion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[3]	1 / 11 (9.09%)	0 / 139 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	17 / 221 (7.69%)	14 / 225 (6.22%)
occurrences (all)	11	34	29
chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	5 / 221 (2.26%)	3 / 225 (1.33%)
occurrences (all)	2	5	3
cyst			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences (all)	1	0	1
fatigue			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	25 / 221 (11.31%)	27 / 225 (12.00%)
occurrences (all)	10	55	51
influenza like illness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	5 / 221 (2.26%)	13 / 225 (5.78%)
occurrences (all)	0	8	17
malaise			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	34 / 221 (15.38%)	19 / 225 (8.44%)
occurrences (all)	0	69	35
mucosal inflammation			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	2 / 14 (14.29%)	14 / 221 (6.33%)	6 / 225 (2.67%)
occurrences (all)	3	28	6
non-cardiac chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	10 / 221 (4.52%)	5 / 225 (2.22%)
occurrences (all)	1	13	5
oedema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	3 / 221 (1.36%)	2 / 225 (0.89%)
occurrences (all)	2	4	2
oedema peripheral			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 14 (35.71%)	50 / 221 (22.62%)	10 / 225 (4.44%)
occurrences (all)	6	78	11
pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	6 / 221 (2.71%)	9 / 225 (4.00%)
occurrences (all)	1	6	10
pyrexia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	45 / 221 (20.36%)	24 / 225 (10.67%)
occurrences (all)	4	57	34
xerosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	7 / 221 (3.17%)	4 / 225 (1.78%)
occurrences (all)	1	9	5
Immune system disorders			
allergy to arthropod sting			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
hypersensitivity			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	2 / 225 (0.89%)
occurrences (all)	1	1	2
Reproductive system and breast disorders			
genital rash			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences (all)	2	2	0
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	48 / 221 (21.72%)	35 / 225 (15.56%)
occurrences (all)	10	62	49
dysphonia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	14 / 221 (6.33%)	2 / 225 (0.89%)
occurrences (all)	2	17	2
dyspnoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	18 / 221 (8.14%)	9 / 225 (4.00%)
occurrences (all)	3	25	9
epistaxis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 14 (35.71%)	74 / 221 (33.48%)	27 / 225 (12.00%)
occurrences (all)	5	102	33
haemoptysis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	11 / 221 (4.98%)	2 / 225 (0.89%)
occurrences (all)	4	19	2
interstitial lung disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	2 / 225 (0.89%)
occurrences (all)	1	1	2
nasal disorder			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences (all)	1	1	0
nasal inflammation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	4 / 221 (1.81%)	4 / 225 (1.78%)
occurrences (all)	4	5	5
oropharyngeal pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	19 / 221 (8.60%)	13 / 225 (5.78%)
occurrences (all)	1	25	14
orthopnoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences (all)	1	1	0
productive cough			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	15 / 221 (6.79%)	11 / 225 (4.89%)
occurrences (all)	0	21	17
rhinorrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	13 / 221 (5.88%)	9 / 225 (4.00%)
occurrences (all)	1	17	9
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	7 / 221 (3.17%)	4 / 225 (1.78%)
occurrences (all)	1	16	5
confusional state			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	0 / 225 (0.00%)
occurrences (all)	1	3	0
depressed mood			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences (all)	1	0	1
depression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	4 / 225 (1.78%)
occurrences (all)	2	2	5
insomnia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	32 / 221 (14.48%)	29 / 225 (12.89%)
occurrences (all)	3	36	33
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	7 / 14 (50.00%)	93 / 221 (42.08%)	70 / 225 (31.11%)
occurrences (all)	12	270	192
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 14 (35.71%)	92 / 221 (41.63%)	58 / 225 (25.78%)
occurrences (all)	7	270	128
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	23 / 221 (10.41%)	20 / 225 (8.89%)
occurrences (all)	2	39	46
blood bilirubin increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	68 / 221 (30.77%)	70 / 225 (31.11%)
occurrences (all)	4	254	251
blood creatinine increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	5 / 221 (2.26%)	6 / 225 (2.67%)
occurrences (all)	1	13	8
blood lactate dehydrogenase increased			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	6 / 221 (2.71%)	2 / 225 (0.89%)
occurrences (all)	1	22	11
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	3 / 221 (1.36%)	4 / 225 (1.78%)
occurrences (all)	2	6	5
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	12 / 221 (5.43%)	7 / 225 (3.11%)
occurrences (all)	2	35	11
neutrophil count decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	25 / 221 (11.31%)	16 / 225 (7.11%)
occurrences (all)	1	83	39
platelet count decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	31 / 221 (14.03%)	6 / 225 (2.67%)
occurrences (all)	5	54	10
transaminases increased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences (all)	1	5	1
weight decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	28 / 221 (12.67%)	29 / 225 (12.89%)
occurrences (all)	2	54	37
white blood cell count decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	14 / 221 (6.33%)	7 / 225 (3.11%)
occurrences (all)	0	53	14
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	6 / 225 (2.67%)
occurrences (all)	1	2	6
infusion related reaction			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	3 / 221 (1.36%)	2 / 225 (0.89%)
occurrences (all)	1	3	2
skin abrasion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences (all)	1	0	1
skin laceration			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	2 / 225 (0.89%)
occurrences (all)	1	1	2
Cardiac disorders			
sinus bradycardia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences (all)	1	3	1
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	20 / 221 (9.05%)	19 / 225 (8.44%)
occurrences (all)	1	27	24
dysgeusia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	39 / 221 (17.65%)	32 / 225 (14.22%)
occurrences (all)	3	46	44
headache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	7 / 14 (50.00%)	33 / 221 (14.93%)	16 / 225 (7.11%)
occurrences (all)	13	56	21
neuralgia			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	2 / 225 (0.89%)
occurrences (all)	1	0	2
paraesthesia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	5 / 225 (2.22%)
occurrences (all)	1	3	5
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	7 / 221 (3.17%)	9 / 225 (4.00%)
occurrences (all)	1	7	10
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	21 / 221 (9.50%)	10 / 225 (4.44%)
occurrences (all)	2	49	15
neutropenia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	3 / 221 (1.36%)	2 / 225 (0.89%)
occurrences (all)	4	9	11
thrombocytopenia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	5 / 221 (2.26%)	0 / 225 (0.00%)
occurrences (all)	6	9	0
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	12 / 221 (5.43%)	4 / 225 (1.78%)
occurrences (all)	0	16	5
Eye disorders			
blepharitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	4 / 221 (1.81%)	9 / 225 (4.00%)
occurrences (all)	1	7	11
dry eye			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	22 / 221 (9.95%)	23 / 225 (10.22%)
occurrences (all)	1	27	24
eyelid oedema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
ocular discomfort			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences (all)	2	0	1
ocular hyperaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	3 / 221 (1.36%)	2 / 225 (0.89%)
occurrences (all)	1	3	2
Gastrointestinal disorders			
abdominal discomfort			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	2 / 225 (0.89%)
occurrences (all)	1	1	2
abdominal pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	15 / 221 (6.79%)	15 / 225 (6.67%)
occurrences (all)	5	26	18
abdominal pain upper			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	17 / 221 (7.69%)	19 / 225 (8.44%)
occurrences (all)	2	23	41
anal fissure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences (all)	1	5	1
anal fistula			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
cheilitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	7 / 221 (3.17%)	5 / 225 (2.22%)
occurrences (all)	1	8	5
constipation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	42 / 221 (19.00%)	31 / 225 (13.78%)
occurrences (all)	3	52	38
dental caries			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	8 / 221 (3.62%)	8 / 225 (3.56%)
occurrences (all)	1	8	8
diarrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	13 / 14 (92.86%)	154 / 221 (69.68%)	160 / 225 (71.11%)
occurrences (all)	57	410	388
dry mouth			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	8 / 221 (3.62%)	3 / 225 (1.33%)
occurrences (all)	1	8	5
dyspepsia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	11 / 221 (4.98%)	12 / 225 (5.33%)
occurrences (all)	1	17	21
dysphagia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	4 / 221 (1.81%)	5 / 225 (2.22%)
occurrences (all)	1	6	6
gastritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	19 / 221 (8.60%)	9 / 225 (4.00%)
occurrences (all)	0	22	11

gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	16 / 221 (7.24%)	9 / 225 (4.00%)
occurrences (all)	1	22	12
gingival bleeding			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	19 / 221 (8.60%)	3 / 225 (1.33%)
occurrences (all)	2	23	3
haemorrhoids			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	14 / 221 (6.33%)	9 / 225 (4.00%)
occurrences (all)	0	19	12
inguinal hernia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
nausea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 14 (28.57%)	57 / 221 (25.79%)	44 / 225 (19.56%)
occurrences (all)	5	81	79
oesophageal pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
rectal haemorrhage			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	2 / 221 (0.90%)	0 / 225 (0.00%)
occurrences (all)	2	2	0
stomatitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	6 / 14 (42.86%)	92 / 221 (41.63%)	82 / 225 (36.44%)
occurrences (all)	13	148	144
tooth disorder			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
toothache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	5 / 221 (2.26%)	1 / 225 (0.44%)
occurrences (all)	1	5	1
vomiting			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 14 (28.57%)	26 / 221 (11.76%)	25 / 225 (11.11%)
occurrences (all)	6	34	31
Hepatobiliary disorders			
hepatitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	0 / 225 (0.00%)
occurrences (all)	1	6	0
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	6 / 14 (42.86%)	75 / 221 (33.94%)	44 / 225 (19.56%)
occurrences (all)	7	84	47
dermatitis acneiform			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	9 / 14 (64.29%)	149 / 221 (67.42%)	153 / 225 (68.00%)
occurrences (all)	33	433	447
dermatitis contact			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	4 / 221 (1.81%)	6 / 225 (2.67%)
occurrences (all)	1	5	10
dry skin			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	9 / 14 (64.29%)	83 / 221 (37.56%)	91 / 225 (40.44%)
occurrences (all)	19	127	181
ecchymosis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
erythema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	12 / 221 (5.43%)	10 / 225 (4.44%)
occurrences (all)	2	83	24
hair disorder			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences (all)	1	2	1
hirsutism			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[4]	1 / 11 (9.09%)	1 / 139 (0.72%)	4 / 142 (2.82%)
occurrences (all)	1	1	4
intertrigo			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences (all)	1	1	0
nail dystrophy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	3 / 225 (1.33%)
occurrences (all)	1	0	3
nail toxicity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	2 / 225 (0.89%)
occurrences (all)	1	0	2
pruritus			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 14 (35.71%)	51 / 221 (23.08%)	66 / 225 (29.33%)
occurrences (all)	12	110	165
purpura			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	11 / 221 (4.98%)	5 / 225 (2.22%)
occurrences (all)	2	17	5

rash			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 14 (35.71%)	39 / 221 (17.65%)	54 / 225 (24.00%)
occurrences (all)	29	103	148
rash macular			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	1 / 225 (0.44%)
occurrences (all)	1	1	1
rash maculo-papular			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 14 (28.57%)	20 / 221 (9.05%)	21 / 225 (9.33%)
occurrences (all)	13	47	53
skin fissures			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	9 / 221 (4.07%)	14 / 225 (6.22%)
occurrences (all)	2	13	19
skin lesion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	2 / 225 (0.89%)
occurrences (all)	2	4	4
xeroderma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences (all)	1	0	1
Renal and urinary disorders			
haematuria			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	10 / 221 (4.52%)	8 / 225 (3.56%)
occurrences (all)	2	11	12
leukocyturia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
proteinuria			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	5 / 14 (35.71%)	75 / 221 (33.94%)	19 / 225 (8.44%)
occurrences (all)	18	278	35
Endocrine disorders			
hypothyroidism			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	3 / 221 (1.36%)	0 / 225 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 14 (35.71%)	8 / 221 (3.62%)	7 / 225 (3.11%)
occurrences (all)	6	9	7
back pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 14 (28.57%)	24 / 221 (10.86%)	17 / 225 (7.56%)
occurrences (all)	6	28	22
muscle spasms			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	9 / 221 (4.07%)	8 / 225 (3.56%)
occurrences (all)	1	12	11
musculoskeletal chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	7 / 221 (3.17%)	12 / 225 (5.33%)
occurrences (all)	1	8	15
musculoskeletal discomfort			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences (all)	2	1	0
musculoskeletal pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 14 (28.57%)	12 / 221 (5.43%)	5 / 225 (2.22%)
occurrences (all)	5	14	5
myalgia			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	5 / 221 (2.26%)	9 / 225 (4.00%)
occurrences (all)	1	10	9
neck pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 14 (21.43%)	6 / 221 (2.71%)	6 / 225 (2.67%)
occurrences (all)	3	8	7
pain in extremity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	9 / 221 (4.07%)	12 / 225 (5.33%)
occurrences (all)	2	9	16
tendonitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 221 (0.45%)	0 / 225 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
angular cheilitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	3 / 221 (1.36%)	6 / 225 (2.67%)
occurrences (all)	1	3	7
bacteriuria			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
candida infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
conjunctivitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	21 / 221 (9.50%)	32 / 225 (14.22%)
occurrences (all)	6	26	40
cystitis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 14 (7.14%)	8 / 221 (3.62%)	9 / 225 (4.00%)
occurrences (all)	1	12	17
eye infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	0 / 225 (0.00%)
occurrences (all)	1	2	0
folliculitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	7 / 221 (3.17%)	11 / 225 (4.89%)
occurrences (all)	1	17	15
gastroenteritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	5 / 221 (2.26%)	4 / 225 (1.78%)
occurrences (all)	1	5	4
gingivitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	6 / 221 (2.71%)	1 / 225 (0.44%)
occurrences (all)	1	16	1
infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
nasopharyngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 14 (35.71%)	22 / 221 (9.95%)	18 / 225 (8.00%)
occurrences (all)	6	27	28
paronychia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	10 / 14 (71.43%)	118 / 221 (53.39%)	114 / 225 (50.67%)
occurrences (all)	24	277	238
parotitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0

perichondritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences (all)	1	0	1
pharyngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	15 / 221 (6.79%)	6 / 225 (2.67%)
occurrences (all)	1	20	7
pulpitis dental			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
rash pustular			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	6 / 221 (2.71%)	14 / 225 (6.22%)
occurrences (all)	0	12	34
respiratory tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	1 / 225 (0.44%)
occurrences (all)	1	0	1
rhinitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	4 / 221 (1.81%)	4 / 225 (1.78%)
occurrences (all)	1	4	4
tinea cruris			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	0 / 225 (0.00%)
occurrences (all)	1	0	0
tonsillitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 221 (0.90%)	1 / 225 (0.44%)
occurrences (all)	1	3	1
upper respiratory tract infection			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	2 / 14 (14.29%)	38 / 221 (17.19%)	34 / 225 (15.11%)
occurrences (all)	5	53	52
urinary tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 14 (14.29%)	17 / 221 (7.69%)	11 / 225 (4.89%)
occurrences (all)	3	23	21
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	4 / 14 (28.57%)	57 / 221 (25.79%)	47 / 225 (20.89%)
occurrences (all)	11	101	84
hypoalbuminaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	14 / 221 (6.33%)	10 / 225 (4.44%)
occurrences (all)	1	27	17
hypokalaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 14 (0.00%)	18 / 221 (8.14%)	5 / 225 (2.22%)
occurrences (all)	0	38	12
hypomagnesaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 221 (0.00%)	2 / 225 (0.89%)
occurrences (all)	1	0	4

Notes:

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported