Clinical trial results:
TIGER-1: A Randomized, Open-Label, Phase 2/3 Study of CO-1686 or Erlotinib as First-Line Treatment of Patients with Epidermal Growth Factor Receptor (EGFR)-Mutant Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2014-000370-19
Trial protocol	DE ES FR IT
Global end of trial date	28 July 2017

Results information

Result version number	v1 (current)
This version publication date	02 June 2019
First version publication date	02 June 2019

Trial information

Trial identification

Sponsor protocol code	CO-1686-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02186301
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clovis Oncology UK Ltd
Sponsor organisation address	Sheraton House, Castle Park, Cambridge, United Kingdom, CB3 0AX
Public contact	Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 1223370037, info@clovisoncology.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2017
Global end of trial reached?	Yes
Global end of trial date	28 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the antitumor efficacy of oral single-agent CO-1686 with that of erlotinib as measured by progression free survival (PFS), when administered as a first line targeted treatment to patients with EGFR-mutated, advanced/metastatic NSCLC

Protection of trial subjects:

A data monitoring committee consisting of 3 of the clinical trial investigators and sponsor personnel met every 3 to 6 months to review and assess the safety and efficacy data, and provide recommendations regarding study continuation/discontinuation and protocol modifications.

Background therapy: -

Evidence for comparator:

Erlotinib is approved in indication under study.

Actual start date of recruitment	01 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	United States: 66
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	100
EEA total number of subjects	1

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)	50
From 65 to 84 years	47
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

100 subjects from 74 sites, in 7 countries randomized (1:1) to treatment with rociletinib or erlotinib. Original protocol had rociletinib starting dose of 625mg BID. In global Amendment 2, starting dose reduced to 500mg BID. Crossover to rociletinib was permitted, however, only 2 subjects did so. Safety data for these 2 subjects are reported.

Pre-assignment

Screening details:

Eligible patients were ≥ 18 years of age with advanced/metastatic NSCLC that had evidence of a tumor with activating EGFR and had undergone a biopsy or surgical resection of either primary or metastatic tumor tissue within 60 days of the first day of study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rociletinib 625mg Tablets

Arm description:

Starting dose of 625mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

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

Dosage and administration details:

Starting dose of 625mg. Taken orally twice daily (continuous daily dosing).

Arm title	Rociletinib 500mg Tablets

Arm description:

Starting dose of 500mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

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

Dosage and administration details:

Starting dose of 500mg. Taken orally twice daily (continuous daily dosing).

Arm title	Erlotinib 150mg Tablets

Arm description:

Starting dose of 150mg. Taken orally once daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Arm type	Active comparator

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

Dosage and administration details:

Starting dose of 150mg. Taken orally once daily (continuous daily dosing).

Number of subjects in period 1	Rociletinib 625mg Tablets	Rociletinib 500mg Tablets	Erlotinib 150mg Tablets
Started	30	20	50
Crossed Over to Rociletinib 500 mg BID	0	0	1
Crossed Over to Rociletinib 625 mg BID	0	0	1
Completed	0	0	0
Not completed	30	20	50
Consent withdrawn by subject	1	5	3
Physician decision	-	1	1
Adverse Event	5	5	5
Death	-	1	-
Progressive Disease	22	7	27
Unknown	-	-	1
Study Terminated by Sponsor	-	1	11
Missing	-	-	2
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Rociletinib 625mg Tablets
Reporting group description:	
Starting dose of 625mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.	

Reporting group title	Rociletinib 500mg Tablets
Reporting group description:	
Starting dose of 500mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.	

Reporting group title	Erlotinib 150mg Tablets
Reporting group description:	
Starting dose of 150mg. Taken orally once daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.	

Reporting group values	Rociletinib 625mg Tablets	Rociletinib 500mg Tablets	Erlotinib 150mg Tablets
Number of subjects	30	20	50
Age categorical Units: Subjects			
Adults (18-64 years)	13	9	28
From 65-84 years	16	10	21
85 years and over	1	1	1
Age continuous Units: years			
median	67	66	64
full range (min-max)	41 to 85	44 to 86	39 to 88
Gender categorical Units: Subjects			
Female	18	17	32
Male	12	3	18
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	0	6
Not Hispanic or Latino	27	19	43
Unknown or Not Reported	0	1	1
Race/Ethnicity, Customized 1 Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	15	9	25
Black or African American	2	2	1
Native Hawaiian or Other Pacific Islander	0	0	0
White	12	9	21
Other	0	0	1
Missing	1	0	2
Race/Ethnicity, Customized 2 Units: Subjects			
White	12	9	21

Asian	15	9	25
Non-White, Non-Asian	3	2	4

Time Since Diagnosis of NSCLC Units: months			
arithmetic mean	5.3	7.2	8.2
standard deviation	± 10.39	± 14.12	± 21.83

Reporting group values	Total		
Number of subjects	100		
Age categorical Units: Subjects			
Adults (18-64 years)	50		
From 65-84 years	47		
85 years and over	3		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	67		
Male	33		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	89		
Unknown or Not Reported	2		
Race/Ethnicity, Customized 1 Units: Subjects			
American Indian or Alaska Native	0		
Asian	49		
Black or African American	5		
Native Hawaiian or Other Pacific Islander	0		
White	42		
Other	1		
Missing	3		
Race/Ethnicity, Customized 2 Units: Subjects			
White	42		
Asian	49		
Non-White, Non-Asian	9		
Time Since Diagnosis of NSCLC Units: months			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Rociletinib 625mg Tablets

Reporting group description:

Starting dose of 625mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Rociletinib 500mg Tablets

Reporting group description:

Starting dose of 500mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Erlotinib 150mg Tablets

Reporting group description:

Starting dose of 150mg. Taken orally once daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Primary: Progression Free Survival (PFS) According to RECIST Version 1.1 as Determined by Investigator Review (invPFS)

End point title	Progression Free Survival (PFS) According to RECIST Version 1.1 as Determined by Investigator Review (invPFS)[1]

End point description:

Median InvPFS was calculated as 1+ the number of days from the date of randomization to documented radiographic progression as determined by the investigator, or death due to any cause, whichever occurs first. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest 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 one or more new lesions is also considered progression. 1 patient in the Chemotherapy treatment group was not included in the analysis, due to discontinuation of study shortly after randomization and prior to first dose of study drug.

End point type	Primary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 35 months. This Time Frame includes the crossover period.

Notes:

[1] - 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 EMA feedback, the statistical analyses section can not accommodate the end point results for this study. Therefore, for each end point, all statistical analyses details are provided in the End point values sections.

End point values	Rociletinib 625mg Tablets	Rociletinib 500mg Tablets	Erlotinib 150mg Tablets	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[2]	18[3]	50[4]	
Units: PFS Days	207	274	390	

Notes:

[2] - PFS Days - Confidence interval: level 95%, 2-sided, lower limit 112, upper limit 260

[3] - PFS Days - Confidence interval: level 95%, 2-sided, lower limit 109, upper limit not available

[4] - PFS Days - Confidence interval: level 95%, 2-sided, lower limit 282, upper limit 499

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Confirmed Response

End point title	Percentage of Patients With Confirmed Response

End point description:

Percentage of patients with a best overall confirmed response of partial response (PR) or complete response (CR) recorded from the start of the treatment until disease progression or recurrence. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for target lesions, defined by and assessed as: Complete Response (CR), is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial Response (PR),at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Overall Response (OR),is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment was dependent on the achievement of both measurement and confirmation criteria.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 35 months. This Time Frame includes the crossover period.

End point values	Rociletinib 625mg Tablets	Rociletinib 500mg Tablets	Erlotinib 150mg Tablets	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[5]	20[6]	50[7]	
Units: Percentage of patients	40	25	78	

Notes:

[5] - Percentage of Patients - Confidence interval: level 95%, 2-sided, lower limit 22.7, upper limit 59.4

[6] - Percentage of Patients - Confidence interval: level 95%, 2-sided, lower limit 8.7, upper limit 49.1

[7] - Percentage of Patients - Confidence interval: level 95%, 2-sided, lower limit 64.0, upper limit 88.5

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) According to RECIST Version 1.1 as Determined by Investigator Assessment

End point title	Duration of Response (DOR) According to RECIST Version 1.1 as Determined by Investigator Assessment

End point description:

Median Duration of Response in patients with confirmed response per investigator. The DOR for complete response (CR) and partial response (PR) was measured from the date that any of these best responses is first recorded until the first date that progressive disease (PD) is objectively documented. For patients who continue treatment post-progression, the first date of progression was used for the analysis.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 35 months

End point values	Rociletinib 625mg Tablets	Rociletinib 500mg Tablets	Erlotinib 150mg Tablets	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12[8]	5[9]	39[10]	
Units: DOR Days	195	225	335	

Notes:

[8] - DOR Days - Confidence interval: level 95%, 2-sided, lower limit 143, upper limit 617

[9] - DOR Days - Confidence interval: level 95%, 2-sided, lower limit 113, upper limit not available

[10] - DOR Days - Confidence interval: level 95%, 2-sided, lower limit 282, upper limit 480

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the date of first dose of study drug and until 28 days after last dose of study drug.

Adverse event reporting additional description:

If a subject experiences the same preferred term (system organ class) multiple times, then the subject will be counted only once for that preferred term (system organ class). Treatment Arm/Groups for the 2 subjects who crossed over to Rociletinib dose groups (1 per group) from Erlotinib are included. However, only 1 crossover subject reported AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Rociletinib 625mg Tablets

Reporting group description:

Starting dose of 625mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Rociletinib 500mg Tablets

Reporting group description:

Starting dose of 500mg. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Erlotinib 150mg Tablets

Reporting group description:

Starting dose of 150mg. Taken orally once daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Crossover From Erlotinib 150mg to Rociletinib 500mg

Reporting group description:

Patients initially randomized to erlotinib were eligible to participate in an optional crossover phase to receive Rociletinib. Starting dose of 500mg Rociletinib. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Crossover From Erlotinib 150mg to Rociletinib 625mg

Reporting group description:

Patients initially randomized to erlotinib were eligible to participate in an optional crossover phase to receive Rociletinib. Starting dose of 625mg Rociletinib. Taken orally twice daily (continuous 28 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Serious adverse events	Rociletinib 625mg Tablets	Rociletinib 500mg Tablets	Erlotinib 150mg Tablets
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 30 (50.00%)	10 / 19 (52.63%)	7 / 50 (14.00%)
number of deaths (all causes)	1	3	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metastases to bone			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute respiratory failure			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranasal cyst			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Pulmonary embolism			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Cardiac murmur			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Femur fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Torsade de pointes			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Nausea			
subjects affected / exposed	0 / 30 (0.00%)	2 / 19 (10.53%)	0 / 50 (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
Pancreatitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 30 (3.33%)	2 / 19 (10.53%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Acute cholangtis, Acute cholecystitis and acute pancreatitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Endocrine disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle spasms			

subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 19 (10.53%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (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
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polydipsia			

subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Crossover From Erlotinib 150mg to Rociletinib 500mg	Crossover From Erlotinib 150mg to Rociletinib 625mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal cyst			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Cardiac murmur			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Torsade de pointes			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericardial effusion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute cholangtis, Acute cholecystitis and acute pancreatitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polydipsia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rociletinib 625mg Tablets	Rociletinib 500mg Tablets	Erlotinib 150mg Tablets
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)	19 / 19 (100.00%)	50 / 50 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	1	1	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	2 / 50 (4.00%)
occurrences (all)	4	1	2
Catheter site haematoma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Catheter site inflammation			

subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Catheter site pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	2 / 50 (4.00%)
occurrences (all)	2	1	2
Chest pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	4 / 50 (8.00%)
occurrences (all)	2	0	4
Chills			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Fatigue			
subjects affected / exposed	9 / 30 (30.00%)	6 / 19 (31.58%)	12 / 50 (24.00%)
occurrences (all)	11	7	16
Malaise			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	5 / 50 (10.00%)
occurrences (all)	1	1	5
Oedema peripheral			
subjects affected / exposed	4 / 30 (13.33%)	2 / 19 (10.53%)	5 / 50 (10.00%)
occurrences (all)	4	3	5
Pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	4
Pyrexia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	2 / 50 (4.00%)
occurrences (all)	3	0	2
Oedema			

subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	1	2	0
Cough			
subjects affected / exposed	6 / 30 (20.00%)	5 / 19 (26.32%)	13 / 50 (26.00%)
occurrences (all)	6	5	14
Dysphonia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Dyspnoea			
subjects affected / exposed	7 / 30 (23.33%)	4 / 19 (21.05%)	7 / 50 (14.00%)
occurrences (all)	8	4	8
Dyspnoea exertional			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	2 / 50 (4.00%)
occurrences (all)	3	1	2
Hypoxia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	4 / 50 (8.00%)
occurrences (all)	2	0	4
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	2 / 19 (10.53%)	1 / 50 (2.00%)
occurrences (all)	2	3	1
Pneumonia aspiration			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 30 (3.33%)	2 / 19 (10.53%)	6 / 50 (12.00%)
occurrences (all)	1	2	7
Upper-airway cough syndrome			

subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Wheezing			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 30 (13.33%)	1 / 19 (5.26%)	7 / 50 (14.00%)
occurrences (all)	4	1	7
Depression			
subjects affected / exposed	6 / 30 (20.00%)	1 / 19 (5.26%)	4 / 50 (8.00%)
occurrences (all)	7	1	4
Insomnia			
subjects affected / exposed	3 / 30 (10.00%)	5 / 19 (26.32%)	7 / 50 (14.00%)
occurrences (all)	3	5	9
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	4 / 50 (8.00%)
occurrences (all)	0	2	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	5 / 50 (10.00%)
occurrences (all)	0	2	7
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	1	1	2
Blood bilirubin increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	5 / 50 (10.00%)
occurrences (all)	0	3	14
Blood cholesterol increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	7 / 30 (23.33%)	2 / 19 (10.53%)	1 / 50 (2.00%)
occurrences (all)	16	2	1
Neutrophil count decreased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Platelet count decreased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	5 / 30 (16.67%)	3 / 19 (15.79%)	4 / 50 (8.00%)
occurrences (all)	10	6	8
White blood cell count decreased			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	5	2	0
Ejection fraction decreased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	3 / 50 (6.00%)
occurrences (all)	0	1	3
Sinus tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 30 (6.67%)	3 / 19 (15.79%)	9 / 50 (18.00%)
occurrences (all)	2	3	11
Headache			

subjects affected / exposed	5 / 30 (16.67%)	2 / 19 (10.53%)	3 / 50 (6.00%)
occurrences (all)	8	2	3
Neuropathy peripheral			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Syncope			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	2 / 50 (4.00%)
occurrences (all)	4	0	3
Dysgeusia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Anaemia			
subjects affected / exposed	2 / 30 (6.67%)	6 / 19 (31.58%)	1 / 50 (2.00%)
occurrences (all)	2	9	1
Leukopenia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Lymphopenia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Cataract			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	3	1	1
Dry eye			

subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	7 / 50 (14.00%)
occurrences (all)	0	0	8
Vision blurred			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 30 (10.00%)	3 / 19 (15.79%)	4 / 50 (8.00%)
occurrences (all)	3	4	6
Abdominal pain upper			
subjects affected / exposed	1 / 30 (3.33%)	3 / 19 (15.79%)	2 / 50 (4.00%)
occurrences (all)	1	6	3
Constipation			
subjects affected / exposed	6 / 30 (20.00%)	3 / 19 (15.79%)	2 / 50 (4.00%)
occurrences (all)	6	3	3
Diarrhoea			
subjects affected / exposed	15 / 30 (50.00%)	7 / 19 (36.84%)	33 / 50 (66.00%)
occurrences (all)	26	12	48
Dry mouth			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	3 / 50 (6.00%)
occurrences (all)	1	1	3
Dyspepsia			
subjects affected / exposed	1 / 30 (3.33%)	4 / 19 (21.05%)	3 / 50 (6.00%)
occurrences (all)	1	5	4
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 30 (10.00%)	2 / 19 (10.53%)	6 / 50 (12.00%)
occurrences (all)	3	2	6
Haemorrhoids			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	8 / 30 (26.67%)	10 / 19 (52.63%)	7 / 50 (14.00%)
occurrences (all)	11	13	8
Stomatitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	9 / 50 (18.00%)
occurrences (all)	3	0	12

Vomiting			
subjects affected / exposed	6 / 30 (20.00%)	5 / 19 (26.32%)	4 / 50 (8.00%)
occurrences (all)	7	5	5
Abdominal discomfort			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Odynophagia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Cholecystitis chronic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Cholelithiasis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	8 / 50 (16.00%)
occurrences (all)	1	0	9
Dermatitis acneiform			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	18 / 50 (36.00%)
occurrences (all)	1	0	37
Dry skin			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	9 / 50 (18.00%)
occurrences (all)	1	0	10
Hyperhidrosis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Pruritus			

subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	6 / 50 (12.00%)
occurrences (all)	2	0	6
Pruritus generalised			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	3 / 30 (10.00%)	4 / 19 (21.05%)	26 / 50 (52.00%)
occurrences (all)	5	5	42
Rash maculo-papular			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Skin fissures			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	4 / 50 (8.00%)
occurrences (all)	0	0	5
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Endocrine disorders			
Tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	3 / 19 (15.79%)	2 / 50 (4.00%)
occurrences (all)	0	3	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 19 (5.26%)	4 / 50 (8.00%)
occurrences (all)	5	2	5
Back pain			
subjects affected / exposed	4 / 30 (13.33%)	0 / 19 (0.00%)	7 / 50 (14.00%)
occurrences (all)	7	0	10
Muscle spasms			
subjects affected / exposed	5 / 30 (16.67%)	5 / 19 (26.32%)	3 / 50 (6.00%)
occurrences (all)	6	9	3
Musculoskeletal chest pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	3 / 50 (6.00%)
occurrences (all)	2	0	3
Musculoskeletal pain			

subjects affected / exposed	1 / 30 (3.33%)	2 / 19 (10.53%)	5 / 50 (10.00%)
occurrences (all)	1	2	5
Myalgia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 19 (10.53%)	1 / 50 (2.00%)
occurrences (all)	2	3	1
Pain in extremity			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	6 / 50 (12.00%)
occurrences (all)	2	0	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Candida infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 19 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	4
Infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 19 (10.53%)	3 / 50 (6.00%)
occurrences (all)	0	2	3
Oral candidiasis			
subjects affected / exposed	3 / 30 (10.00%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Oral herpes			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	10 / 50 (20.00%)
occurrences (all)	1	0	12
Pneumonia			
subjects affected / exposed	3 / 30 (10.00%)	2 / 19 (10.53%)	2 / 50 (4.00%)
occurrences (all)	4	2	2

Upper respiratory tract infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 19 (0.00%)	8 / 50 (16.00%)
occurrences (all)	1	0	12
Urinary tract infection			
subjects affected / exposed	4 / 30 (13.33%)	0 / 19 (0.00%)	6 / 50 (12.00%)
occurrences (all)	4	0	6
Vaginal infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 30 (16.67%)	5 / 19 (26.32%)	9 / 50 (18.00%)
occurrences (all)	5	5	12
Dehydration			
subjects affected / exposed	3 / 30 (10.00%)	3 / 19 (15.79%)	1 / 50 (2.00%)
occurrences (all)	3	3	1
Diabetic ketoacidosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	15 / 30 (50.00%)	10 / 19 (52.63%)	2 / 50 (4.00%)
occurrences (all)	28	23	2
Hyperkalaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 19 (5.26%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Hypocalcaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Hypomagnesaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 19 (5.26%)	2 / 50 (4.00%)
occurrences (all)	1	1	3
Hyponatraemia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 19 (10.53%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Polydipsia			

subjects affected / exposed	2 / 30 (6.67%)	0 / 19 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Hypokalaemia			
subjects affected / exposed	2 / 30 (6.67%)	3 / 19 (15.79%)	0 / 50 (0.00%)
occurrences (all)	3	4	0

Non-serious adverse events	Crossover From Erlotinib 150mg to Rociletinib 500mg	Crossover From Erlotinib 150mg to Rociletinib 625mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Catheter site haematoma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Catheter site inflammation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Catheter site pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Chest discomfort			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	3	
Malaise			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Mucosal inflammation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Oedema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
Dysphonia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			

subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
Dyspnoea exertional			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hypoxia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pleural effusion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pneumonia aspiration			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Wheezing			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Blood creatinine increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Platelet count decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
White blood cell count decreased			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Ejection fraction decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Sinus tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Anaemia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Lymphopenia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dry eye			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
Diarrhoea			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dry mouth			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Abdominal discomfort			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Odynophagia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Cholecystitis chronic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

Cholelithiasis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dermatitis acneiform			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hyperhidrosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pruritus generalised			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Skin fissures			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			

Renal failure acute			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Candida infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

Conjunctivitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Paronychia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Vaginal infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Dehydration			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hyperkalaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hyponatraemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Polydipsia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2015	In global Amendment 1 (Version 2.0), a Phase 3 part was added and randomization of an additional 1,000 patients was allowed.
23 April 2015	In global Amendment 2 (Version 3.0), the dose of rociletinib was decreased from 625 mg BID to 500 mg BID. Emerging data from the first-in-human study showed that whilst there was no difference in efficacy, 500 mg BID provided better tolerability than 625 mg BID. For Amendment 2, there were also country-specific addenda in Germany (Version 3.1, 23 July 2015 and Version 3.2, 12 August 2015), to specify closer monitoring of electrocardiogram (ECG) parameters and to clarify patients required to undergo an End-of-Treatment scan, and South Korea (Version 3.1, 23 April 2015) specifying that rociletinib may cause hyperglycemia in some patients and to provide monitoring guidelines.
22 August 2016	In a global Amendment 3 (Version 4.0), details regarding the discontinuation of clinical development of rociletinib were provided; an extension phase was added allowing patients to continue on study if they were deriving clinical benefit and removing the option for patients to crossover to rociletinib following radiographic progression on erlotinib. In addition, the availability of N-acetyltransferase 2 testing for patients, an indirect indicator of the likelihood of developing hyperglycemia and QT interval corrected for heart rate (QTc) prolongation, was introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 December 2015	On 16 December 2015, investigators were notified of early enrollment closure based on the de-prioritization of the rociletinib clinical development program. No new patients were permitted to consent effective 24 December 2015 or were randomized effective 05 February 2016. Due to early closure, 100 patients were included in Phase 2 and no patients were enrolled in Phase 3.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For two end points, Progression Free Survival and Duration of Response, the Statistical Analysis upper Confidence Limits are not available because they could not be calculated.

Notes: