Clinical trial results:
TIGER-2: A Phase 2, Open-label, Multicenter, Safety and Efficacy Study of Oral CO-1686 as 2nd Line EGFR-directed TKI in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2013-005532-23
Trial protocol	DE ES NL
Global end of trial date	27 August 2019

Results information

Result version number	v1 (current)
This version publication date	06 September 2020
First version publication date	06 September 2020

Trial information

Trial identification

Sponsor protocol code	CO-1686-019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02147990
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clovis Oncology UK Ltd
Sponsor organisation address	Granta Centre, Granta Park, Great Abington, Cambridge, United Kingdom, CB21 6GP
Public contact	Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 12233645500, lrolfe@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	26 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2019
Global end of trial reached?	Yes
Global end of trial date	27 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor efficacy of oral (PO) single-agent rociletinib, as measured by objective response rate (ORR), when administered to patients with EGFR-mutated, centrally confirmed T790M-positive and T790M-negative advanced NSCLC after tumor progression on 1 previous EGFR-directed TKI

Protection of trial subjects:

Safety assessments during treatment included monitoring for adverse events (AEs), laboratory tests (hematology, clinical chemistry including fasting glucose and glycated hemoglobin [HbA1c], and urinalysis), physical examinations, vital signs and body weight measurements, 12-lead ECG (triplicate recordings), concomitant medications/procedures, and ECOG performance status on Day 1 of each cycle.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 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	Netherlands: 23
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 28
Country: Number of subjects enrolled	United States: 127
Worldwide total number of subjects	317
EEA total number of subjects	88

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)	164
From 65 to 84 years	147
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

318 patients were enrolled at 67 study sites in North America, Europe, Asia and Australia. One patient was not included in the Safety Population due to failure of the study site to provide any dosing data in electronic data capture (EDC) before the site was closed.

Pre-assignment

Screening details:

All patients underwent screening assessments within 28 days prior to the first dose of rociletinib to establish study eligibility and document baseline measurements. Eligible NSCLC patients were required to have documented evidence of a tumor with an EGFR mutation known to be associated with sensitivity to rociletinib.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rociletinib 625 mg BID T790M+

Arm description:

Rociletinib 625 mg BID in patients with T790M-positive tumor status

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 rociletinib, taken orally twice daily, with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Tablets should be swallowed whole. Treatment with rociletinib was continuous and each cycle was comprised of 28 days.

Arm title	Rociletinib 500 mg BID T790M+

Arm description:

Rociletinib 500 mg BID in patients with T790M-positive tumor status

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 rociletinib, taken orally twice daily, with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Tablets should be swallowed whole. Treatment with rociletinib was continuous and each cycle was comprised of 28 days.

Arm title	Rociletinib 500 mg BID T790M-

Arm description:

Rociletinib 500 mg BID in patients with T790M-negative tumor status

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 rociletinib, taken orally twice daily, with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Tablets should be swallowed whole. Treatment with rociletinib was continuous and each cycle was comprised of 28 days.

Number of subjects in period 1	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-
Started	154	100	63
Completed	154	100	63

Baseline characteristics

Reporting groups	
Reporting group title	Rociletinib 625 mg BID T790M+
Reporting group description:	
Rociletinib 625 mg BID in patients with T790M-positive tumor status	
Reporting group title	Rociletinib 500 mg BID T790M+
Reporting group description:	
Rociletinib 500 mg BID in patients with T790M-positive tumor status	
Reporting group title	Rociletinib 500 mg BID T790M-
Reporting group description:	
Rociletinib 500 mg BID in patients with T790M-negative tumor status	

Reporting group values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-
Number of subjects	154	100	63
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	62.8	65.3	64.1
standard deviation	± 10.67	± 9.93	± 10.01
Gender categorical Units: Subjects			
Female	105	69	41
Male	49	31	22
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	3
Not Hispanic or Latino	131	93	55
Unknown or Not Reported	21	5	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	59	34	32
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	5	2
White	74	58	23

More than one race	0	0	0
Unknown or Not Reported	14	3	6
T790M Status			
Units: Subjects			
T790M Negative	1	0	62
T790M Positive	153	100	0
Missing	0	0	1

Reporting group values	Total		
Number of subjects	317		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	215		
Male	102		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	279		
Unknown or Not Reported	31		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	125		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	13		
White	155		
More than one race	0		
Unknown or Not Reported	23		
T790M Status			
Units: Subjects			
T790M Negative	63		
T790M Positive	253		
Missing	1		

Subject analysis sets	
Subject analysis set title	All T790M+
Subject analysis set type	Per protocol

Subject analysis set description:

All Rociletinib 500 mg BID and 625 mg BID patients with T790M positive tumor status

Reporting group values	All T790M+		
Number of subjects	254		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	63.8		
standard deviation	± 10.43		
Gender categorical Units: Subjects			
Female	174		
Male	80		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	224		
Unknown or Not Reported	26		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	93		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	11		
White	132		
More than one race	0		
Unknown or Not Reported	17		
T790M Status Units: Subjects			
T790M Negative	1		
T790M Positive	253		
Missing	0		

End points

End points reporting groups

Reporting group title	Rociletinib 625 mg BID T790M+
Reporting group description: Rociletinib 625 mg BID in patients with T790M-positive tumor status	
Reporting group title	Rociletinib 500 mg BID T790M+
Reporting group description: Rociletinib 500 mg BID in patients with T790M-positive tumor status	
Reporting group title	Rociletinib 500 mg BID T790M-
Reporting group description: Rociletinib 500 mg BID in patients with T790M-negative tumor status	
Subject analysis set title	All T790M+
Subject analysis set type	Per protocol
Subject analysis set description: All Rociletinib 500 mg BID and 625 mg BID patients with T790M positive tumor status	

Primary: Objective Response Rate (ORR) According to RECIST Version 1.1 as Determined by Investigator Assessment

End point title	Objective Response Rate (ORR) According to RECIST Version 1.1 as Determined by Investigator Assessment[1]

End point description:

ORR is defined as the 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. For patients who continued treatment post-progression, the first date of progression was used for the analysis. 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.

End point type	Primary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 57 months

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, all statistical analyses details are provided in the End point values sections.

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	97	61	
Units: Percentage of Patients				
number (confidence interval 95%)	34.6 (27.1 to 42.7)	34.0 (24.7 to 44.3)	18.0 (9.4 to 30.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) in T790M Positive Patients According to RECIST Version 1.1 as Determined by Investigator Assessment

End point title	Duration of Response (DOR) in T790M Positive Patients According to RECIST Version 1.1 as Determined by Investigator Assessment[2]

End point description:

DOR in patients with a T790M mutation (determined by central lab) 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:

From Cycle 1 Day 1 until disease progression or end of treatment, whichever came first, assessed up to 54 months

Notes:

[2] - 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: This endpoint reports results for T790M Positive Patients only.

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	All T790M+	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	53	33	86	
Units: Months				
median (confidence interval 95%)	7.4 (5.5 to 9.4)	9.1 (5.6 to 13.0)	7.6 (7.3 to 9.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) by RECIST v1.1 as Determined by Investigator Assessment

End point title	Disease Control Rate (DCR) by RECIST v1.1 as Determined by Investigator Assessment

End point description:

DCR is defined as the percentage of patients who have achieved CR, PR, and SD lasting at least 12 weeks. 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. Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum longest diameter since the treatment started.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 until disease progression or end of treatment, whichever came first, assessed up to 57 months

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	97	61	
Units: Percentage of Patients				
number (confidence interval 95%)	67.3 (59.3 to 74.7)	76.3 (66.6 to 84.3)	59.0 (45.7 to 71.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) in T790M Positive Patients by RECIST v1.1 as Determined by Investigator Assessment

End point title	Progression-free Survival (PFS) in T790M Positive Patients by RECIST v1.1 as Determined by Investigator Assessment[3]

End point description:

PFS was calculated as 1+ the number of days from the first dose of study drug to documented radiographic progression or death due to any cause, whichever occurs first. Patients without a documented event of radiographic progression were censored on the date of their last adequate tumor assessment (i.e., radiologic assessment) or date of first dose of study drug if no tumor assessments were performed. For patients who continued treatment post-progression, the first date of progression was used for the analysis of PFS. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), 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 new lesions is also considered progression.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 until disease progression or end of treatment, whichever came first, assessed up to 57 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports results for T790M Positive Patients only.

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	All T790M+	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	154	100	254	
Units: Months				
median (confidence interval 95%)	5.5 (4.0 to 6.7)	5.9 (5.3 to 8.3)	5.5 (5.3 to 7.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Determined by Investigator Assessment

End point title	Overall Survival (OS) Determined by Investigator

End point description:

OS was calculated as 1+ the number of days from the first dose of study drug to death due to any cause. Patients without a documented date of death were censored on the date the patient was last known to be alive.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to date of death, assessed up to 57 months

Notes:

[4] - 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: This endpoint reports results for T790M Positive Patients only.

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	All T790M+	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	154[5]	100[6]	254	
Units: Months				
median (confidence interval 95%)	18.8 (15.2 to 57)	29.8 (26.2 to 47)	23.7 (17.7 to 40.6)	

Notes:

[5] - Upper confidence interval not available due to insufficient number of participants so max 57 noted.

[6] - Upper confidence interval not available due to insufficient number of participants so max 47 noted.

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-C30 Global Health Status

End point title	EORTC QLQ-C30 Global Health Status

End point description:

EORTC QLC-C30 is a 30-item questionnaire to assess the quality of life in cancer patients. EORTC QLQ-C30 includes functional scales (physical, role, cognitive, emotional, social), global health status, symptom scales (fatigue, pain, nausea/vomiting), and other (dyspnoea, appetite loss, insomnia, constipation/diarrhea, financial difficulties). Most questions used 4-point scale (1 'Not at All' to 4 'Very Much'); two used 7-point scale (1 'Very Poor' to 7'Excellent'). Scores are averaged, and transformed to 0-100 scale; higher score = better quality of life. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[7]	100[8]	63[9]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	62.18 (± 22.245)	59.76 (± 22.495)	54.63 (± 24.629)	
Cycle 5 (approximately month 5)	-2.48 (± 22.470)	-0.56 (± 23.763)	5.56 (± 28.842)	
Cycle 10 (approximately month 10)	-2.21 (± 22.294)	-3.81 (± 21.422)	3.57 (± 23.956)	
End of Treatment	-4.82 (± 23.381)	-9.65 (± 18.481)	-10.42 (± 35.158)	

Notes:

[7] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 49, EOT = 38

[8] - Baseline = 99, Cycle 5 = 60, Cycle 10 = 35, EOT = 19

[9] - Baseline = 63, Cycle 5 = 33, Cycle 10 = 14, EOT = 16

Statistical analyses

No statistical analyses for this end point

Secondary: Dermatology Life Quality Index (DLQI)

End point title	Dermatology Life Quality Index (DLQI)

End point description:

Dermatology Life Quality Index (DLQI) score is a participant-reported outcome consisting of a set of 10 questions regarding the degree to which the participant's skin has affected certain behaviors and quality of life over the last week. Responses to each are: very much (score of 3), a lot, a little, or not at all (score of 0). The DLQI score ranges from 0 (best) to 30 (worst); the higher the score, the more quality of life is impaired. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[10]	100[11]	63[12]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	2.10 (± 3.408)	2.42 (± 4.706)	2.74 (± 4.763)	
Cycle 5 (approximately month 5)	-0.82 (± 3.240)	-1.29 (± 3.499)	-1.63 (± 3.731)	
Cycle 10 (approximately month 10)	-1.02 (± 2.810)	-1.64 (± 3.531)	-0.79 (± 2.751)	
End of Treatment	-0.77 (± 3.191)	-0.22 (± 2.157)	-1.14 (± 4.204)	

Notes:

[10] - Baseline = 152, Cycle 5 = 97, Cycle 10 = 49, EOT = 35

[11] - Baseline = 97, Cycle 5 = 58, Cycle 10 = 36, EOT = 18

[12] - Baseline = 62, Cycle 5 = 32, Cycle 10 = 14, EOT = 14

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Alopecia Scale

End point title	EORTC QLQ-LC-13 Alopecia Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[13]	100[14]	63[15]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	9.96 (± 21.264)	9.43 (± 20.779)	19.05 (± 29.154)	
Cycle 5 (approximately month 5)	-4.62 (± 27.499)	-2.69 (± 27.855)	-10.10 (± 19.516)	
Cycle 10 (approximately month 10)	-2.00 (± 21.728)	-6.67 (± 25.309)	-2.56 (± 21.350)	
End of Treatment	4.50 (± 33.483)	3.51 (± 44.298)	0.00 (± 39.841)	

Notes:

[13] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 50, EOT = 37

[14] - Baseline = 99, Cycle 5 = 62, Cycle 10 = 35, EOT = 19

[15] - Baseline = 63, Cycle 5 = 33, Cycle 10 = 13, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Coughing Scale

End point title	EORTC QLQ-LC-13 Coughing Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related

symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[16]	100[17]	63[18]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	33.12 (± 26.540)	29.97 (± 25.862)	38.62 (± 23.346)	
Cycle 5 (approximately month 5)	-7.92 (± 26.728)	-9.29 (± 26.619)	-12.12 (± 27.409)	
Cycle 10 (approximately month 10)	-6.67 (± 23.328)	-17.14 (± 30.648)	2.56 (± 21.350)	
End of Treatment	-5.41 (± 27.793)	0.00 (± 36.851)	6.67 (± 25.820)	

Notes:

[16] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 50, EOT = 37

[17] - Baseline = 99, Cycle 5 = 61, Cycle 10 = 35, EOT = 19

[18] - Baseline = 63, Cycle 5 = 33, Cycle 10 = 13, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Dysphagia Scale

End point title	EORTC QLQ-LC-13 Dysphagia Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[19]	100[20]	63[21]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	5.19 (± 15.306)	7.41 (± 17.532)	5.82 (± 17.495)	
Cycle 5 (approximately month 5)	1.65 (± 12.803)	-0.54 (± 17.589)	7.07 (± 21.663)	
Cycle 10 (approximately month 10)	-3.27 (± 13.752)	-3.81 (± 15.700)	2.56 (± 9.245)	
End of Treatment	3.60 (± 17.184)	7.41 (± 31.427)	6.67 (± 28.730)	

Notes:

[19] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 51, EOT = 37

[20] - Baseline = 99, Cycle 5 = 62, Cycle 10 = 35, EOT = 18

[21] - Baseline = 63, Cycle 5 = 33, Cycle 10 = 13, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Dyspnoea Scale

End point title	EORTC QLQ-LC-13 Dyspnoea Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[22]	100[23]	63[24]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	21.79 (± 21.554)	22.56 (± 21.441)	30.34 (± 26.415)	
Cycle 5 (approximately month 5)	6.11 (± 21.681)	-1.25 (± 18.777)	-3.70 (± 23.516)	
Cycle 10 (approximately month 10)	2.83 (± 19.606)	1.90 (± 14.879)	6.84 (± 22.923)	
End of Treatment	8.41 (± 22.892)	8.77 (± 18.362)	0.00 (± 28.172)	

Notes:

[22] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 51, EOT = 37

[23] - Baseline = 99, Cycle 5 = 62, Cycle 10 = 35, EOT = 19

[24] - Baseline = 63, Cycle 5 = 33, Cycle 10 = 13, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Haemoptysis Scale

End point title	EORTC QLQ-LC-13 Haemoptysis Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[25]	100[26]	63[27]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	2.38 (± 8.613)	1.68 (± 11.039)	4.76 (± 13.194)	
Cycle 5 (approximately month 5)	-1.98 (± 7.919)	-1.61 (± 9.404)	-5.21 (± 14.930)	
Cycle 10 (approximately month 10)	-0.65 (± 8.138)	-0.95 (± 5.634)	-5.13 (± 18.490)	
End of Treatment	-0.90 (± 12.389)	0.00 (± 0.000)	-2.22 (± 8.607)	

Notes:

[25] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 51, EOT = 37

[26] - Baseline = 99, Cycle 5 = 62, Cycle 10 = 35, EOT = 19

[27] - Baseline = 63, Cycle 5 = 32, Cycle 10 = 13, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Pain in Arm or Shoulder Scale

End point title	EORTC QLQ-LC-13 Pain in Arm or Shoulder Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related

symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[28]	100[29]	63[30]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	19.91 (± 26.271)	16.67 (± 26.325)	28.42 (± 34.338)	
Cycle 5 (approximately month 5)	-5.94 (± 32.110)	-2.69 (± 25.819)	-7.29 (± 35.655)	
Cycle 10 (approximately month 10)	-1.31 (± 31.242)	-2.86 (± 27.262)	8.33 (± 28.868)	
End of Treatment	5.41 (± 29.932)	0.00 (± 35.136)	4.44 (± 33.014)	

Notes:

[28] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 51, EOT = 37

[29] - Baseline = 98, Cycle 5 = 62, Cycle 10 = 35, EOT = 19

[30] - Baseline = 61, Cycle 5 = 32, Cycle 10 = 12, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Pain in Chest Scale

End point title	EORTC QLQ-LC-13 Pain in Chest Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[31]	100[32]	63[33]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	19.91 (± 25.429)	12.79 (± 22.691)	25.40 (± 32.635)	
Cycle 5 (approximately month 5)	-4.62 (± 25.399)	-5.38 (± 20.194)	-8.08 (± 28.904)	
Cycle 10 (approximately month 10)	-3.27 (± 24.272)	-6.86 (± 19.728)	2.56 (± 39.585)	
End of Treatment	1.80 (± 34.198)	7.02 (± 13.962)	-4.44 (± 30.516)	

Notes:

[31] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 51, EOT = 37

[32] - Baseline = 99, Cycle 5 = 62, Cycle 10 = 34, EOT = 19

[33] - Baseline = 63, Cycle 5 = 33, Cycle 10 = 13, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Medicine for Pain Scale

End point title	EORTC QLQ-LC-13 Medicine for Pain Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[34]	100[35]	63[36]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	60.47 (± 27.302)	66.67 (± 27.766)	53.17 (± 23.350)	
Cycle 5 (approximately month 5)	6.67 (± 35.450)	8.89 (± 23.458)	-4.76 (± 36.648)	
Cycle 10 (approximately month 10)	4.76 (± 12.105)	-4.17 (± 27.817)	22.22 (± 19.245)	
End of Treatment	3.92 (± 20.008)	0.00 (± 30.861)	-5.56 (± 38.968)	

Notes:

[34] - Baseline = 86, Cycle 5 = 30, Cycle 10 = 14, EOT = 17

[35] - Baseline = 50, Cycle 5 = 15, Cycle 10 = 8, EOT = 8

[36] - Baseline = 42, Cycle 5 = 14, Cycle 10 = 3, EOT = 6

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Pain in Other Parts Scale

End point title	EORTC QLQ-LC-13 Pain in Other Parts Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[37]	100[38]	63[39]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	28.41 (± 30.848)	30.58 (± 33.219)	31.69 (± 29.456)	
Cycle 5 (approximately month 5)	2.46 (± 34.464)	-1.13 (± 29.664)	-7.78 (± 33.543)	
Cycle 10 (approximately month 10)	-3.47 (± 28.550)	-6.67 (± 31.102)	-2.78 (± 22.285)	
End of Treatment	20.59 (± 31.798)	0.00 (± 26.352)	6.67 (± 44.006)	

Notes:

[37] - Baseline = 149, Cycle 5 = 95, Cycle 10 = 48, EOT = 34

[38] - Baseline = 97, Cycle 5 = 59, Cycle 10 = 35, EOT = 17

[39] - Baseline = 61, Cycle 5 = 30, Cycle 10 = 12, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Peripheral Neuropathy Scale

End point title	EORTC QLQ-LC-13 Peripheral Neuropathy Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related

symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[40]	100[41]	63[42]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	11.90 (± 22.117)	6.40 (± 17.611)	17.20 (± 29.409)	
Cycle 5 (approximately month 5)	0.00 (± 25.386)	3.76 (± 23.458)	4.17 (± 31.395)	
Cycle 10 (approximately month 10)	4.58 (± 25.837)	2.86 (± 18.737)	0.00 (± 20.101)	
End of Treatment	2.70 (± 21.341)	7.02 (± 26.244)	2.22 (± 15.258)	

Notes:

[40] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 51, EOT = 37

[41] - Baseline = 99, Cycle 5 = 62, Cycle 10 = 35, EOT = 19

[42] - Baseline = 62, Cycle 5 = 32, Cycle 10 = 12, EOT = 15

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC-13 Sore Mouth Scale

End point title	EORTC QLQ-LC-13 Sore Mouth Scale

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms. Change from Baseline to Cycles 5, 10 and End of Treatment is reported.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 5, 10 and EOT

End point values	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[43]	100[44]	63[45]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Day 0)	5.19 (± 13.273)	7.41 (± 17.532)	10.58 (± 21.440)	
Cycle 5 (approximately month 5)	1.98 (± 18.149)	-2.19 (± 21.832)	-2.02 (± 27.562)	
Cycle 10 (approximately month 10)	0.65 (± 19.425)	-1.90 (± 24.176)	2.56 (± 21.350)	
End of Treatment	4.50 (± 21.026)	12.28 (± 29.836)	2.22 (± 36.659)	

Notes:

[43] - Baseline = 154, Cycle 5 = 101, Cycle 10 = 51, EOT = 37

[44] - Baseline = 99, Cycle 5 = 61, Cycle 10 = 35, EOT = 19

[45] - Baseline = 63, Cycle 5 = 33, Cycle 10 = 13, EOT = 15

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 within 28 days after last dose of study drug, or up to approximately 62 months. In addition, study procedure-related AEs that occurred after signing of the informed consent form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Rociletinib 625 mg BID T790M+
Reporting group description:	
Rociletinib 625 mg BID in patients with T790M-positive tumor status	
Reporting group title	Rociletinib 500 mg BID T790M+
Reporting group description:	
Rociletinib 500 mg BID in patients with T790M-positive tumor status	
Reporting group title	Rociletinib 500 mg BID T790M-
Reporting group description:	
Rociletinib 500 mg BID in patients with T790M-negative tumor status	

Serious adverse events	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 154 (50.00%)	48 / 100 (48.00%)	34 / 63 (53.97%)
number of deaths (all causes)	27	7	9
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	23 / 154 (14.94%)	4 / 100 (4.00%)	7 / 63 (11.11%)
occurrences causally related to treatment / all	0 / 24	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 23	0 / 3	0 / 7
Malignant pleural effusion			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			

subjects affected / exposed	1 / 154 (0.65%)	1 / 100 (1.00%)	0 / 63 (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
Myelodysplastic syndrome			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Embolism			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Shock haemorrhagic			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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			
Chest pain			
subjects affected / exposed	2 / 154 (1.30%)	2 / 100 (2.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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

Euthanasia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Fatigue			
subjects affected / exposed	0 / 154 (0.00%)	2 / 100 (2.00%)	0 / 63 (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
Malaise			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
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			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Oedema			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
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			
subjects affected / exposed	1 / 154 (0.65%)	3 / 100 (3.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			

subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
Chylothorax			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 154 (0.65%)	4 / 100 (4.00%)	3 / 63 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Hypoxia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 154 (0.65%)	2 / 100 (2.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			

subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 154 (0.65%)	1 / 100 (1.00%)	0 / 63 (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
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Confusional state			
subjects affected / exposed	2 / 154 (1.30%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 154 (1.30%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Transaminases increased			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Injury, poisoning and procedural			

complications			
Postoperative ileus			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Traumatic fracture			
subjects affected / exposed	1 / 154 (0.65%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 154 (1.30%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pericarditis			
subjects affected / exposed	2 / 154 (1.30%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Cognitive disorder			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Epilepsy			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukoencephalopathy			

subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Partial seizures			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 154 (1.30%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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	3 / 154 (1.95%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Thrombocytopenia			
subjects affected / exposed	2 / 154 (1.30%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 154 (0.00%)	2 / 100 (2.00%)	0 / 63 (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
Cataract			

subjects affected / exposed	2 / 154 (1.30%)	2 / 100 (2.00%)	4 / 63 (6.35%)
occurrences causally related to treatment / all	1 / 2	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 154 (1.30%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Colitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Constipation			
subjects affected / exposed	3 / 154 (1.95%)	2 / 100 (2.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 154 (1.95%)	4 / 100 (4.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 3	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 154 (0.65%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	6 / 154 (3.90%)	2 / 100 (2.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	5 / 7	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	5 / 154 (3.25%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	4 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 154 (2.60%)	3 / 100 (3.00%)	3 / 63 (4.76%)
occurrences causally related to treatment / all	5 / 5	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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	0 / 154 (0.00%)	0 / 100 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 154 (0.65%)	2 / 100 (2.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder obstruction			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Hepatic function abnormal			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Hepatitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder perforation			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Cystitis interstitial			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	3 / 154 (1.95%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Flank pain			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscular weakness			
subjects affected / exposed	0 / 154 (0.00%)	2 / 100 (2.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 154 (0.65%)	1 / 100 (1.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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			
Biliary tract infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Clostridium difficile infection			

subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Cystitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Diverticulitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Influenza			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Listeria sepsis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 100 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	3 / 154 (1.95%)	5 / 100 (5.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 3	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 154 (0.00%)	2 / 100 (2.00%)	0 / 63 (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
Sepsis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 154 (0.00%)	3 / 100 (3.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 154 (0.65%)	0 / 100 (0.00%)	0 / 63 (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
Dehydration			

subjects affected / exposed	4 / 154 (2.60%)	2 / 100 (2.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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	10 / 154 (6.49%)	6 / 100 (6.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	13 / 13	7 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 100 (1.00%)	0 / 63 (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			
subjects affected / exposed	1 / 154 (0.65%)	1 / 100 (1.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 154 (0.65%)	1 / 100 (1.00%)	0 / 63 (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

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

Non-serious adverse events	Rociletinib 625 mg BID T790M+	Rociletinib 500 mg BID T790M+	Rociletinib 500 mg BID T790M-
Total subjects affected by non-serious adverse events			
subjects affected / exposed	153 / 154 (99.35%)	100 / 100 (100.00%)	63 / 63 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	27 / 154 (17.53%)	7 / 100 (7.00%)	9 / 63 (14.29%)
occurrences (all)	35	8	11

Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 154 (5.84%)	4 / 100 (4.00%)	3 / 63 (4.76%)
occurrences (all)	12	4	5
Hypotension			
subjects affected / exposed	5 / 154 (3.25%)	5 / 100 (5.00%)	0 / 63 (0.00%)
occurrences (all)	5	5	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 154 (12.34%)	6 / 100 (6.00%)	6 / 63 (9.52%)
occurrences (all)	34	10	8
Chest pain			
subjects affected / exposed	11 / 154 (7.14%)	13 / 100 (13.00%)	3 / 63 (4.76%)
occurrences (all)	13	14	3
Fatigue			
subjects affected / exposed	57 / 154 (37.01%)	48 / 100 (48.00%)	29 / 63 (46.03%)
occurrences (all)	89	86	46
Influenza like illness			
subjects affected / exposed	8 / 154 (5.19%)	5 / 100 (5.00%)	2 / 63 (3.17%)
occurrences (all)	13	6	2
Malaise			
subjects affected / exposed	4 / 154 (2.60%)	2 / 100 (2.00%)	4 / 63 (6.35%)
occurrences (all)	4	2	4
Mucosal inflammation			
subjects affected / exposed	6 / 154 (3.90%)	7 / 100 (7.00%)	3 / 63 (4.76%)
occurrences (all)	6	11	3
Non-cardiac chest pain			
subjects affected / exposed	8 / 154 (5.19%)	1 / 100 (1.00%)	2 / 63 (3.17%)
occurrences (all)	9	1	2
Oedema peripheral			
subjects affected / exposed	16 / 154 (10.39%)	6 / 100 (6.00%)	8 / 63 (12.70%)
occurrences (all)	21	7	9
Pyrexia			
subjects affected / exposed	21 / 154 (13.64%)	11 / 100 (11.00%)	5 / 63 (7.94%)
occurrences (all)	25	15	7
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	35 / 154 (22.73%)	25 / 100 (25.00%)	18 / 63 (28.57%)
occurrences (all)	43	25	18
Dysphonia			
subjects affected / exposed	2 / 154 (1.30%)	6 / 100 (6.00%)	2 / 63 (3.17%)
occurrences (all)	2	6	2
Dyspnoea			
subjects affected / exposed	28 / 154 (18.18%)	24 / 100 (24.00%)	15 / 63 (23.81%)
occurrences (all)	41	34	18
Dyspnoea exertional			
subjects affected / exposed	5 / 154 (3.25%)	6 / 100 (6.00%)	1 / 63 (1.59%)
occurrences (all)	6	7	1
Haemoptysis			
subjects affected / exposed	4 / 154 (2.60%)	0 / 100 (0.00%)	4 / 63 (6.35%)
occurrences (all)	4	0	4
Pleural effusion			
subjects affected / exposed	7 / 154 (4.55%)	6 / 100 (6.00%)	6 / 63 (9.52%)
occurrences (all)	7	7	10
Productive cough			
subjects affected / exposed	8 / 154 (5.19%)	4 / 100 (4.00%)	4 / 63 (6.35%)
occurrences (all)	9	7	5
Rhinorrhoea			
subjects affected / exposed	2 / 154 (1.30%)	5 / 100 (5.00%)	0 / 63 (0.00%)
occurrences (all)	2	5	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 154 (4.55%)	4 / 100 (4.00%)	4 / 63 (6.35%)
occurrences (all)	7	4	4
Confusional state			
subjects affected / exposed	8 / 154 (5.19%)	3 / 100 (3.00%)	2 / 63 (3.17%)
occurrences (all)	10	4	3
Depression			
subjects affected / exposed	5 / 154 (3.25%)	6 / 100 (6.00%)	3 / 63 (4.76%)
occurrences (all)	5	6	3
Insomnia			

subjects affected / exposed	13 / 154 (8.44%)	10 / 100 (10.00%)	6 / 63 (9.52%)
occurrences (all)	16	11	6
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 154 (13.64%)	9 / 100 (9.00%)	6 / 63 (9.52%)
occurrences (all)	35	14	10
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 154 (11.69%)	5 / 100 (5.00%)	5 / 63 (7.94%)
occurrences (all)	29	10	8
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 154 (6.49%)	6 / 100 (6.00%)	4 / 63 (6.35%)
occurrences (all)	13	9	4
Blood bilirubin increased			
subjects affected / exposed	15 / 154 (9.74%)	3 / 100 (3.00%)	2 / 63 (3.17%)
occurrences (all)	32	4	2
Blood creatinine increased			
subjects affected / exposed	12 / 154 (7.79%)	7 / 100 (7.00%)	5 / 63 (7.94%)
occurrences (all)	18	9	10
Electrocardiogram QT prolonged			
subjects affected / exposed	62 / 154 (40.26%)	29 / 100 (29.00%)	19 / 63 (30.16%)
occurrences (all)	157	67	37
Platelet count decreased			
subjects affected / exposed	6 / 154 (3.90%)	2 / 100 (2.00%)	4 / 63 (6.35%)
occurrences (all)	17	2	6
Weight decreased			
subjects affected / exposed	43 / 154 (27.92%)	28 / 100 (28.00%)	15 / 63 (23.81%)
occurrences (all)	89	45	19
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 154 (13.64%)	18 / 100 (18.00%)	7 / 63 (11.11%)
occurrences (all)	24	19	8
Dysgeusia			
subjects affected / exposed	10 / 154 (6.49%)	9 / 100 (9.00%)	5 / 63 (7.94%)
occurrences (all)	13	13	5
Headache			

subjects affected / exposed	45 / 154 (29.22%)	19 / 100 (19.00%)	14 / 63 (22.22%)
occurrences (all)	58	27	20
Lethargy			
subjects affected / exposed	3 / 154 (1.95%)	2 / 100 (2.00%)	4 / 63 (6.35%)
occurrences (all)	3	2	6
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 154 (20.78%)	13 / 100 (13.00%)	10 / 63 (15.87%)
occurrences (all)	72	23	21
Neutropenia			
subjects affected / exposed	3 / 154 (1.95%)	5 / 100 (5.00%)	2 / 63 (3.17%)
occurrences (all)	8	7	4
Thrombocytopenia			
subjects affected / exposed	11 / 154 (7.14%)	1 / 100 (1.00%)	1 / 63 (1.59%)
occurrences (all)	28	1	1
Eye disorders			
Cataract			
subjects affected / exposed	28 / 154 (18.18%)	18 / 100 (18.00%)	7 / 63 (11.11%)
occurrences (all)	43	29	13
Vision blurred			
subjects affected / exposed	7 / 154 (4.55%)	8 / 100 (8.00%)	2 / 63 (3.17%)
occurrences (all)	9	8	3
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 154 (3.90%)	6 / 100 (6.00%)	0 / 63 (0.00%)
occurrences (all)	7	6	0
Abdominal pain			
subjects affected / exposed	24 / 154 (15.58%)	15 / 100 (15.00%)	6 / 63 (9.52%)
occurrences (all)	34	21	7
Abdominal pain upper			
subjects affected / exposed	18 / 154 (11.69%)	9 / 100 (9.00%)	1 / 63 (1.59%)
occurrences (all)	26	14	2
Constipation			
subjects affected / exposed	38 / 154 (24.68%)	35 / 100 (35.00%)	21 / 63 (33.33%)
occurrences (all)	53	54	24
Diarrhoea			

subjects affected / exposed	91 / 154 (59.09%)	59 / 100 (59.00%)	30 / 63 (47.62%)
occurrences (all)	192	107	46
Dry mouth			
subjects affected / exposed	18 / 154 (11.69%)	13 / 100 (13.00%)	2 / 63 (3.17%)
occurrences (all)	19	14	2
Dyspepsia			
subjects affected / exposed	13 / 154 (8.44%)	4 / 100 (4.00%)	7 / 63 (11.11%)
occurrences (all)	15	5	8
Gastrooesophageal reflux disease			
subjects affected / exposed	16 / 154 (10.39%)	8 / 100 (8.00%)	5 / 63 (7.94%)
occurrences (all)	16	9	6
Mouth ulceration			
subjects affected / exposed	2 / 154 (1.30%)	2 / 100 (2.00%)	5 / 63 (7.94%)
occurrences (all)	2	2	6
Nausea			
subjects affected / exposed	86 / 154 (55.84%)	58 / 100 (58.00%)	31 / 63 (49.21%)
occurrences (all)	164	87	53
Stomatitis			
subjects affected / exposed	9 / 154 (5.84%)	5 / 100 (5.00%)	1 / 63 (1.59%)
occurrences (all)	9	9	2
Vomiting			
subjects affected / exposed	62 / 154 (40.26%)	35 / 100 (35.00%)	21 / 63 (33.33%)
occurrences (all)	101	45	36
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	11 / 154 (7.14%)	8 / 100 (8.00%)	2 / 63 (3.17%)
occurrences (all)	11	10	2
Pruritus			
subjects affected / exposed	8 / 154 (5.19%)	5 / 100 (5.00%)	7 / 63 (11.11%)
occurrences (all)	13	5	9
Rash			
subjects affected / exposed	9 / 154 (5.84%)	9 / 100 (9.00%)	2 / 63 (3.17%)
occurrences (all)	9	11	2
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	22 / 154 (14.29%)	18 / 100 (18.00%)	5 / 63 (7.94%)
occurrences (all)	26	21	7
Back pain			
subjects affected / exposed	16 / 154 (10.39%)	19 / 100 (19.00%)	9 / 63 (14.29%)
occurrences (all)	18	22	10
Muscle spasms			
subjects affected / exposed	35 / 154 (22.73%)	23 / 100 (23.00%)	10 / 63 (15.87%)
occurrences (all)	49	46	19
Musculoskeletal chest pain			
subjects affected / exposed	11 / 154 (7.14%)	7 / 100 (7.00%)	4 / 63 (6.35%)
occurrences (all)	15	9	4
Musculoskeletal pain			
subjects affected / exposed	13 / 154 (8.44%)	7 / 100 (7.00%)	4 / 63 (6.35%)
occurrences (all)	16	8	4
Myalgia			
subjects affected / exposed	15 / 154 (9.74%)	4 / 100 (4.00%)	1 / 63 (1.59%)
occurrences (all)	17	4	1
Neck pain			
subjects affected / exposed	4 / 154 (2.60%)	5 / 100 (5.00%)	2 / 63 (3.17%)
occurrences (all)	4	5	2
Pain in extremity			
subjects affected / exposed	8 / 154 (5.19%)	7 / 100 (7.00%)	3 / 63 (4.76%)
occurrences (all)	8	8	3
Infections and infestations			
Paronychia			
subjects affected / exposed	2 / 154 (1.30%)	5 / 100 (5.00%)	0 / 63 (0.00%)
occurrences (all)	2	10	0
Pneumonia			
subjects affected / exposed	7 / 154 (4.55%)	5 / 100 (5.00%)	5 / 63 (7.94%)
occurrences (all)	7	5	5
Upper respiratory tract infection			
subjects affected / exposed	13 / 154 (8.44%)	8 / 100 (8.00%)	4 / 63 (6.35%)
occurrences (all)	13	8	4
Urinary tract infection			

subjects affected / exposed	22 / 154 (14.29%)	15 / 100 (15.00%)	6 / 63 (9.52%)
occurrences (all)	29	24	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	62 / 154 (40.26%)	42 / 100 (42.00%)	25 / 63 (39.68%)
occurrences (all)	94	61	37
Dehydration			
subjects affected / exposed	16 / 154 (10.39%)	5 / 100 (5.00%)	2 / 63 (3.17%)
occurrences (all)	16	5	2
Hyperglycaemia			
subjects affected / exposed	97 / 154 (62.99%)	64 / 100 (64.00%)	33 / 63 (52.38%)
occurrences (all)	303	198	116
Hypoalbuminaemia			
subjects affected / exposed	8 / 154 (5.19%)	3 / 100 (3.00%)	3 / 63 (4.76%)
occurrences (all)	13	3	3
Hypokalaemia			
subjects affected / exposed	18 / 154 (11.69%)	9 / 100 (9.00%)	8 / 63 (12.70%)
occurrences (all)	24	12	10
Hypomagnesaemia			
subjects affected / exposed	12 / 154 (7.79%)	7 / 100 (7.00%)	3 / 63 (4.76%)
occurrences (all)	20	7	3
Hyponatraemia			
subjects affected / exposed	8 / 154 (5.19%)	8 / 100 (8.00%)	3 / 63 (4.76%)
occurrences (all)	9	11	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2014	The starting rociletinib dose of 750 mg BID was adjusted to 625 mg BID, and dose modification steps were changed to reflect the reduction of starting dose to 625 mg BID. The addition of a C1D15 ECG safety assessment to identify patients that may be experiencing QTc prolongation resulting from treatment with rociletinib.
27 October 2014	Patients who discontinued treatment prior to progression were to continue to have tumor scans per protocol schedule of every 8 ± 1 weeks until progression; patients with clinical progression of disease were to have radiographic confirmation to document that radiographic progression had occurred.
13 March 2015	The rationale and study design were changed with the addition of a secondary goal to determine the effectiveness of rociletinib in patients with T790M-negative NSCLC, and the addition of a reduced dose level (500 mg BID).
16 August 2016	The Extension Phase was introduced following discontinuation of the rociletinib clinical development program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported