Clinical trial results:
A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2011-005215-86
Trial protocol	PL
Global end of trial date	27 August 2018

Results information

Result version number	v1
This version publication date	04 July 2019
First version publication date	04 July 2019

Trial information

Trial identification

Sponsor protocol code	CO-1686-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01526928
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
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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	27 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2018
Global end of trial reached?	Yes
Global end of trial date	27 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1:
To evaluate the toxicity profile of escalating doses of CO-1686 and to determine the MTD and RP2D
To characterize the PK profile of CO-1686

Phase 2:
To evaluate tumor response (ORR + duration of response) to CO-1686 in patients with T790M

Protection of trial subjects:

Safety measures in Phase 1 included monitoring for dose limiting toxicities (DLTs), as specified in the protocol, that occurred during Cycle 1 in patients enrolled into a DLT-evaluable cohort and were assessed by the investigator as probably, possibly or definitively related to rociletinib, as well as monitoring for adverse events (AEs). Safety measures in Phase 2 included monitoring of AEs, clinical laboratory evaluations, physical examination, vital signs and body weight, 12-lead ECGs, ECOG performance status, and concomitant medications and procedures. Patients were monitored for AEs from the time the first dose of rociletinib was administered through 28 days after the last dose (End of Treatment Visit), including study procedure-related AEs that occurred after signing of the informed consent and before administration of rociletinib. Any ongoing serious AEs were followed until resolution or stabilization. Quality of Life assessments were performed at baseline, every 2 cycles through Cycle 6, and then every 3 cycles thereafter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2012
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	Poland: 5
Country: Number of subjects enrolled	France: 61
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	United States: 518
Worldwide total number of subjects	612
EEA total number of subjects	66

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)	327
From 65 to 84 years	272
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

There were 612 patients who received rociletinib—111 enrolled in Phase 1 and 501 enrolled in Phase 2. The Phase 1 component of the study was conducted at 8 study sites in the US, Australia, and France. Phase 2 was conducted at 49 study sites in the US, France, Poland, and Australia.

Pre-assignment

Screening details:

Phase 1 - Eligible patients were required to have documented evidence of an EGFR-activating mutation, but enrollment into Phase 1 was irrespective of T790M status. Phase 2 - Eligible patients were those who were confirmed by the sponsor's central laboratory or by local assessment to have the T790M mutation in tumor tissue.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rociletinib <900 mg BID FB Capsules

Arm description:

Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID).

Arm type	Experimental
Investigational medicinal product name	Rociletinib free base (FB) capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Rociletinib free base (FB) capsule doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID). Rociletinib free base (FB) capsules were administered in Phase 1 only (until November 2013) and were provided in 50 mg or 150 mg white capsules. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day treatment cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

Arm title	Rociletinib 900 mg BID FB Capsules

Arm description:

Rociletinib free base (FB) dose 900 mg twice a day (BID)

Arm type	Experimental
Investigational medicinal product name	Rociletinib free base (FB) capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Rociletinib free base (FB) dose 900 mg twice a day (BID). Rociletinib FB capsules were administered in Phase 1 only (until November 2013) and were provided in 50 mg or 150 mg white capsules. Patients

were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day treatment cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

Arm title	Rociletinib 500 mg BID HBr Tablets

Arm description:

Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID)

Arm type	Experimental
Investigational medicinal product name	Rociletinib hydrobromide (HBr) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after ameal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

Arm title	Rociletinib 625 mg BID HBr Tablets

Arm description:

Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID)

Arm type	Experimental
Investigational medicinal product name	Rociletinib hydrobromide (HBr) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 625 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after ameal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

Arm title	Rociletinib 750 mg BID HBr Tablets

Arm description:

Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID)

Arm type	Experimental
Investigational medicinal product name	Rociletinib hydrobromide (HBr) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

Arm title	Rociletinib 1000 mg BID HBr Tablets

Arm description:

Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID)

Arm type	Experimental
Investigational medicinal product name	Rociletinib hydrobromide (HBr) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

Number of subjects in period 1	Rociletinib <900 mg BID FB Capsules	Rociletinib 900 mg BID FB Capsules	Rociletinib 500 mg BID HBr Tablets
Started	38	19	209
Completed	0	0	0
Not completed	38	19	209
Consent withdrawn by subject	1	-	13
Physician decision	-	-	2
Adverse Event	2	1	29
Death	-	-	3
Progressive Disease	35	17	150
Unknown	-	1	11
Lost to follow-up	-	-	-
Missing	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	Rociletinib 625 mg BID HBr Tablets	Rociletinib 750 mg BID HBr Tablets	Rociletinib 1000 mg BID HBr Tablets
Started	245	95	6

Completed	0	0	0
Not completed	245	95	6
Consent withdrawn by subject	11	3	-
Physician decision	5	-	-
Adverse Event	40	13	2
Death	-	-	-
Progressive Disease	182	76	4
Unknown	4	1	-
Lost to follow-up	1	-	-
Missing	-	2	-
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Rociletinib <900 mg BID FB Capsules
Reporting group description:	
Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID).	
Reporting group title	Rociletinib 900 mg BID FB Capsules
Reporting group description:	
Rociletinib free base (FB) dose 900 mg twice a day (BID)	
Reporting group title	Rociletinib 500 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID)	
Reporting group title	Rociletinib 625 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID)	
Reporting group title	Rociletinib 750 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID)	
Reporting group title	Rociletinib 1000 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID)	

Reporting group values	Rociletinib <900 mg BID FB Capsules	Rociletinib 900 mg BID FB Capsules	Rociletinib 500 mg BID HBr Tablets
Number of subjects	38	19	209
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	61.5	59.0	65.0
full range (min-max)	34.0 to 83.0	46.0 to 73.0	26.0 to 90.0
Gender categorical Units: Subjects			
Female	31	15	155
Male	7	4	54
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	5
Not Hispanic or Latino	30	15	170
Unknown or Not Reported	6	2	34
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	5	4	41
Native Hawaiian or Other Pacific Islander	0	0	4

Black or African American	0	0	7
White	27	13	122
More than one race	0	0	0
Unknown or Not Reported	6	2	35
Race/Ethnicity, Customized Units: Subjects			
White	27	13	122
Black or African American	0	0	7
Asian	5	4	41
Other	6	2	39
T790M Status (Determined by Central Lab) Units: Subjects			
Negative	5	4	6
Positive	23	9	188
Unknown	10	6	4
Missing	0	0	11
History of CNS Metastases Units: Subjects			
Yes	20	7	86
No	18	12	123
Time Since Diagnosis of NSCLC Units: months			
arithmetic mean	40.4	45.4	36.7
standard deviation	± 29.2	± 31.94	± 25.81
Number of Previous Therapies Units: Therapies			
arithmetic mean	3.8	3.7	2.6
standard deviation	± 1.65	± 1.66	± 1.74
Number of Previous TKI Therapies Units: Therapies			
arithmetic mean	1.7	2.3	1.5
standard deviation	± 0.77	± 1.48	± 0.87

Reporting group values	Rociletinib 625 mg BID HBr Tablets	Rociletinib 750 mg BID HBr Tablets	Rociletinib 1000 mg BID HBr Tablets
Number of subjects	245	95	6
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	64.0	62.0	64.5
full range (min-max)	29.0 to 86.0	30.0 to 85.0	60.0 to 74.0
Gender categorical Units: Subjects			
Female	155	63	5
Male	90	32	1

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	2	0
Not Hispanic or Latino	184	90	6
Unknown or Not Reported	47	3	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	49	24	1
Native Hawaiian or Other Pacific Islander	3	0	0
Black or African American	8	2	0
White	137	64	5
More than one race	1	0	0
Unknown or Not Reported	46	5	0
Race/Ethnicity, Customized Units: Subjects			
White	137	64	5
Black or African American	8	2	0
Asian	49	24	1
Other	51	5	0
T790M Status (Determined by Central Lab) Units: Subjects			
Negative	25	9	0
Positive	176	80	4
Unknown	1	1	2
Missing	43	5	0
History of CNS Metastases Units: Subjects			
Yes	107	44	3
No	138	51	3
Time Since Diagnosis of NSCLC Units: months			
arithmetic mean	36.7	37.6	47.4
standard deviation	± 31.41	± 29.97	± 27.03
Number of Previous Therapies Units: Therapies			
arithmetic mean	2.8	2.9	3.8
standard deviation	± 1.91	± 2.11	± 2.04
Number of Previous TKI Therapies Units: Therapies			
arithmetic mean	1.6	1.6	1.8
standard deviation	± 0.77	± 0.86	± 0.75

Reporting group values	Total		
Number of subjects	612		
Age categorical Units: Subjects			
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		

Age continuous Units: years median full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	424		
Male	188		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	25		
Not Hispanic or Latino	495		
Unknown or Not Reported	92		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	124		
Native Hawaiian or Other Pacific Islander	7		
Black or African American	17		
White	368		
More than one race	1		
Unknown or Not Reported	94		
Race/Ethnicity, Customized Units: Subjects			
White	368		
Black or African American	17		
Asian	124		
Other	103		
T790M Status (Determined by Central Lab) Units: Subjects			
Negative	49		
Positive	480		
Unknown	24		
Missing	59		
History of CNS Metastases Units: Subjects			
Yes	267		
No	345		
Time Since Diagnosis of NSCLC Units: months arithmetic mean standard deviation	 -		
Number of Previous Therapies Units: Therapies arithmetic mean standard deviation	 -		
Number of Previous TKI Therapies Units: Therapies arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Rociletinib <900 mg BID FB Capsules
Reporting group description:	
Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID).	
Reporting group title	Rociletinib 900 mg BID FB Capsules
Reporting group description:	
Rociletinib free base (FB) dose 900 mg twice a day (BID)	
Reporting group title	Rociletinib 500 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID)	
Reporting group title	Rociletinib 625 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID)	
Reporting group title	Rociletinib 750 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID)	
Reporting group title	Rociletinib 1000 mg BID HBr Tablets
Reporting group description:	
Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID)	

Primary: Percentage of T790M Positive Patients With Confirmed Response Per Investigator

End point title	Percentage of T790M Positive Patients With Confirmed Response Per Investigator[1]
End point description:	
Percentage of patients with a T790M mutation (determined by central lab) 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. Analysis Population Description - Intent-to-treat: All randomized patients who are confirmed by central lab to be T790M positive.	
End point type	Primary
End point timeframe:	
Cycle 1 Day 1 to End of Treatment, up to approximately 42 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, for each end point, all statistical analyses details are provided in the End point values sections.

End point values	Rociletinib <900 mg BID FB Capsules	Rociletinib 900 mg BID FB Capsules	Rociletinib 500 mg BID HBr Tablets	Rociletinib 625 mg BID HBr Tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[2]	9[3]	188[4]	176[5]
Units: Percentage of Patients	0	33	29	41

Notes:

[2] - 0/23 = 0.0%; 95% Confidence Interval = 0.0 - 14.8%

[3] - 3/9 = 33.3%; 95% Confidence Interval = 7.5 - 70.1%

[4] - 54/188 = 28.7%; 95% Confidence Interval = 22.4 - 35.8%

[5] - 72/176 = 40.9%; 95% Confidence Interval = 33.6 - 48.6%

End point values	Rociletinib 750 mg BID HBr Tablets	Rociletinib 1000 mg BID HBr Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[6]	4[7]		
Units: Percentage of Patients	29	75		

Notes:

[6] - 23/80 = 28.8%; 95% Confidence Interval = 19.2 - 40.0%

[7] - 3/4 = 75.0%; 95% Confidence Interval = 19.4 - 99.4%

Statistical analyses

No statistical analyses for this end point

Primary: 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[8][9]

End point description:

Duration of Response 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. Analysis Population Description - The DOR was measured only in those patients with a Complete Response (CR) or Partial Response (PR). As this was a Phase 1/2 dose-finding study, data is presented only for the two recommended Phase 2 dose levels, 500 mg BID and 625 mg BID.

End point type	Primary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 36 months

Notes:

[8] - 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.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As this was a Phase 1/2 dose-finding study, data is presented only for the two recommended Phase 2 dose levels, 500 mg BID and 625 mg BID.

End point values	Rociletinib 500 mg BID HBr Tablets	Rociletinib 625 mg BID HBr Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54[10]	72[11]		
Units: Median DOR in Days	275	274		

Notes:

[10] - Median (95% Confidence Interval) = 275 days (226 to 336)

[11] - Median (95% Confidence Interval) = 274 days (169 to 337)

Statistical analyses

No statistical analyses for this end point

Secondary: QTcF Values Post Baseline by Daily Dose

End point title	QTcF Values Post Baseline by Daily Dose

End point description:

Frequency of QT interval prolongation by daily dose (corrected using Fridericia's method, QTcF). To evaluate the effects of rociletinib on the QT (interval from Q wave to T wave)/QTc (interval corrected for heart rate) interval, all patients underwent serial ECG monitoring at Baseline, on Cycle 1 Day 1, Cycle 1 Day 15, on Day 1 of all subsequent cycles, at the EOT Visit, and as clinically indicated. Worst post-baseline QTcF value was used to categorize each patient. Analysis Population Description - Safety population by daily dose.

End point type	Secondary

End point timeframe:

Screening to End of Treatment, up to approximately 42 months

End point values	Rociletinib <900 mg BID FB Capsules	Rociletinib 900 mg BID FB Capsules	Rociletinib 500 mg BID HBr Tablets	Rociletinib 625 mg BID HBr Tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	19	209	245
Units: Participants				
QTcF Post-Baseline <450 msec	34	10	93	99
QTcF Post-Baseline 450-480 msec	4	7	71	93
QTcF Post-Baseline 481-500 msec	0	1	23	24
QTcF Post-Baseline >=501 msec	0	1	22	29

End point values	Rociletinib 750 mg BID HBr Tablets	Rociletinib 1000 mg BID HBr Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	6		
Units: Participants				
QTcF Post-Baseline <450 msec	35	2		
QTcF Post-Baseline 450-480 msec	30	2		
QTcF Post-Baseline 481-500 msec	11	2		
QTcF Post-Baseline >=501 msec	19	0		

Statistical analyses

No statistical analyses for this end point

Secondary: QtcF Value Change From Baseline

End point title	QtcF Value Change From Baseline

End point description:

QTcF value change from baseline by daily dose (corrected using Fridericia's method, QTcF). To evaluate the effects of rociletinib on the QT (interval from Q wave to T wave)/QTc (interval corrected for heart rate) interval, all patients underwent serial ECG monitoring at Baseline, on Cycle 1 Day 1, Cycle 1 Day 15, on Day 1 of all subsequent cycles, at the EOT Visit, and as clinically indicated. Worst post-baseline QTcF value was used to categorize each patient. Analysis Population Description - Safety population by daily dose.

End point type	Secondary

End point timeframe:

Screening to End of Treatment, up to approximately 42 months

End point values	Rociletinib <900 mg BID FB Capsules	Rociletinib 900 mg BID FB Capsules	Rociletinib 500 mg BID HBr Tablets	Rociletinib 625 mg BID HBr Tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	19	209	245
Units: Participants				
QTcF Change from Baseline <=30 msec	29	11	47	55
QTcF Change from Baseline 30-60 msec	9	8	104	101
QTcF Change from Baseline >60 msec	0	0	58	89

End point values	Rociletinib 750 mg BID HBr Tablets	Rociletinib 1000 mg BID HBr Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	6		
Units: Participants				
QTcF Change from Baseline <=30 msec	12	1		
QTcF Change from Baseline 30-60 msec	39	3		
QTcF Change from Baseline >60 msec	44	2		

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 approximately 9 months.

Adverse event reporting additional description:

In addition, study procedure-related AEs that occur after signing of the informed consent form and before first dose of study drug were expected to be reported. Any Serious Adverse Events or Adverse Events of Special Interest were followed until resolution or stabilization, or until patient is lost to follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Rociletinib <900 mg BID FB Capsules

Reporting group description:

Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID).

Reporting group title	Rociletinib 900 mg BID FB Capsules

Reporting group description:

Rociletinib free base (FB) dose 900 mg twice a day (BID)

Reporting group title	Rociletinib 500 mg BID HBr Tablets

Reporting group description:

Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID)

Reporting group title	Rociletinib 625 mg BID HBr Tablets

Reporting group description:

Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID)

Reporting group title	Rociletinib 750 mg BID HBr Tablets

Reporting group description:

Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID)

Reporting group title	Rociletinib 1000 mg BID HBr Tablets

Reporting group description:

Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID)

Serious adverse events	Rociletinib <900 mg BID FB Capsules	Rociletinib 900 mg BID FB Capsules	Rociletinib 500 mg BID HBr Tablets
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 38 (36.84%)	8 / 19 (42.11%)	106 / 209 (50.72%)
number of deaths (all causes)	4	4	31
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
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	8 / 38 (21.05%)	5 / 19 (26.32%)	25 / 209 (11.96%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 28
deaths causally related to treatment / all	0 / 4	0 / 4	0 / 23
Malignant pleural effusion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Metastases to skin			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Hypotension			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Subgaleal haematoma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Venous thrombosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	4 / 209 (1.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Hypersensitivity			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aspiration			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cough			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Dyspnoea			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	8 / 209 (3.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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

Interstitial lung disease			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Lung disorder			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Pleural effusion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Pneumonitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	3 / 209 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (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 distress			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Blood creatinine increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
General physical condition abnormal			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lipase increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (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
Hip fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (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
Jaw fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Radiation necrosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Radiation pneumonitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Rib fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Subcutaneous haematoma			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Subdural haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Bradycardia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Cardiac arrest			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Cardiac failure congestive			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Pericardial effusion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
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	1 / 38 (2.63%)	0 / 19 (0.00%)	0 / 209 (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
Sinus tachycardia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Torsade de pointes			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Ventricular tachyarrhythmia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Nervous system disorders			
Basilar artery thrombosis			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
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 / 38 (0.00%)	0 / 19 (0.00%)	3 / 209 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Disturbance in attention			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord oedema			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Syncope			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	4 / 209 (1.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal dilatation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Intestinal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
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	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	5 / 209 (2.39%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	5 / 209 (2.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	7 / 209 (3.35%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Bile duct stone			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Liver injury			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Nephrolithiasis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Back pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Pathological fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Spinal pain			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Cellulitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Device related infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Endocarditis			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
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			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Hepatic infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Influenza			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Liver abscess			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
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 / 38 (5.26%)	0 / 19 (0.00%)	7 / 209 (3.35%)
occurrences causally related to treatment / all	0 / 3	0 / 0	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
Pneumonia bacterial			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Pneumonia influenzal			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Postoperative wound infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Sepsis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	4 / 209 (1.91%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Septic shock			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Serratia bacteraemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	3 / 209 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
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			
Decreased appetite			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	4 / 209 (1.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Glucose tolerance impaired			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Hypercalcaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Hyperglycaemia			

subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	21 / 209 (10.05%)
occurrences causally related to treatment / all	1 / 1	0 / 0	22 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	0 / 209 (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
Hypokalaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (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
Hyponatraemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	5 / 209 (2.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Rociletinib 625 mg BID HBr Tablets	Rociletinib 750 mg BID HBr Tablets	Rociletinib 1000 mg BID HBr Tablets
Total subjects affected by serious adverse events			
subjects affected / exposed	138 / 245 (56.33%)	54 / 95 (56.84%)	5 / 6 (83.33%)
number of deaths (all causes)	40	19	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Cancer pain			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Malignant neoplasm progression			
subjects affected / exposed	37 / 245 (15.10%)	21 / 95 (22.11%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 38	0 / 22	0 / 1
deaths causally related to treatment / all	0 / 34	0 / 17	0 / 1

Malignant pleural effusion			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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 skin			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Neoplasm malignant			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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	3 / 245 (1.22%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Subgaleal haematoma			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Venous thrombosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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			
Asthenia			
subjects affected / exposed	2 / 245 (0.82%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Non-cardiac chest pain			
subjects affected / exposed	3 / 245 (1.22%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (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
Pyrexia			
subjects affected / exposed	3 / 245 (1.22%)	1 / 95 (1.05%)	0 / 6 (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

Sudden death			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Vaginal haemorrhage			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Aspiration			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Cough			

subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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	10 / 245 (4.08%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Epistaxis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Haemoptysis			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Hypoxia			
subjects affected / exposed	2 / 245 (0.82%)	1 / 95 (1.05%)	0 / 6 (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
Interstitial lung disease			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Lung disorder			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Pleural effusion			

subjects affected / exposed	5 / 245 (2.04%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 245 (0.82%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	4 / 245 (1.63%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	5 / 245 (2.04%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Pulmonary haemorrhage			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Pulmonary hypertension			

subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Respiratory distress			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Respiratory failure			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Confusional state			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Hallucination			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Mental status changes			
subjects affected / exposed	0 / 245 (0.00%)	2 / 95 (2.11%)	0 / 6 (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
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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 creatinine increased			

subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 245 (0.82%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
General physical condition abnormal			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Lipase increased			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Transaminases increased			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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			
Fall			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Femoral neck fracture			

subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Hip fracture			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Jaw fracture			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Radiation necrosis			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Radiation pneumonitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Subcutaneous haematoma			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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 haemorrhage			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Atrial fibrillation			
subjects affected / exposed	1 / 245 (0.41%)	2 / 95 (2.11%)	0 / 6 (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
Atrial tachycardia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Palpitations			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	3 / 245 (1.22%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Sinus tachycardia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Torsade de pointes			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Ventricular tachyarrhythmia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Nervous system disorders			
Basilar artery thrombosis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Brain oedema			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Cerebrovascular accident			

subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Coma			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Disturbance in attention			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Dizziness			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Headache			
subjects affected / exposed	2 / 245 (0.82%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Seizure			
subjects affected / exposed	1 / 245 (0.41%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord oedema			

subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Status epilepticus			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Syncope			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Transient ischaemic attack			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 245 (0.82%)	2 / 95 (2.11%)	0 / 6 (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
Lymphadenopathy			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	4 / 245 (1.63%)	3 / 95 (3.16%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	6 / 6	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 245 (2.86%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Ascites			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Colitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Constipation			
subjects affected / exposed	3 / 245 (1.22%)	1 / 95 (1.05%)	0 / 6 (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
Diarrhoea			
subjects affected / exposed	5 / 245 (2.04%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	3 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 245 (0.82%)	2 / 95 (2.11%)	0 / 6 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Intestinal dilatation			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Intestinal obstruction			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Melaena			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Nausea			
subjects affected / exposed	6 / 245 (2.45%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 6	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Pancreatitis			

subjects affected / exposed	4 / 245 (1.63%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	3 / 4	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Small intestinal perforation			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Subileus			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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	7 / 245 (2.86%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	3 / 7	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			

subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Bile duct stone			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Cholecystitis			
subjects affected / exposed	3 / 245 (1.22%)	1 / 95 (1.05%)	0 / 6 (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
Cholecystitis acute			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Cholelithiasis			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (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
Hepatic pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Liver injury			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (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
Haematuria			

subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Nephrolithiasis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Back pain			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Bursitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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

Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Muscular weakness			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Musculoskeletal chest pain			
subjects affected / exposed	3 / 245 (1.22%)	1 / 95 (1.05%)	0 / 6 (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
Pain in extremity			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Pathological fracture			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (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
Spinal pain			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Bacteraemia			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Clostridium difficile infection			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Endocarditis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Gastroenteritis			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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 infection			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Influenza			

subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Liver abscess			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Lung infection			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Pneumonia			
subjects affected / exposed	10 / 245 (4.08%)	7 / 95 (7.37%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 12	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Pneumonia bacterial			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Pyelonephritis			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (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
Sepsis			

subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Septic shock			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Serratia bacteraemia			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 245 (1.22%)	1 / 95 (1.05%)	0 / 6 (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
Urosepsis			
subjects affected / exposed	3 / 245 (1.22%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Dehydration			
subjects affected / exposed	7 / 245 (2.86%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 7	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			

subjects affected / exposed	3 / 245 (1.22%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (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
Fluid overload			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Glucose tolerance impaired			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Hypercalcaemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (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
Hyperglycaemia			
subjects affected / exposed	19 / 245 (7.76%)	7 / 95 (7.37%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	21 / 21	9 / 9	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 245 (0.00%)	2 / 95 (2.11%)	0 / 6 (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
Hyponatraemia			

subjects affected / exposed	4 / 245 (1.63%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Rociletinib <900 mg BID FB Capsules	Rociletinib 900 mg BID FB Capsules	Rociletinib 500 mg BID HBr Tablets
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 38 (97.37%)	19 / 19 (100.00%)	208 / 209 (99.52%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	11 / 38 (28.95%)	5 / 19 (26.32%)	28 / 209 (13.40%)
occurrences (all)	11	8	32
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	2	0	0
Hypertension			
subjects affected / exposed	5 / 38 (13.16%)	0 / 19 (0.00%)	16 / 209 (7.66%)
occurrences (all)	5	0	34
Hypotension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	4 / 209 (1.91%)
occurrences (all)	0	1	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 38 (15.79%)	1 / 19 (5.26%)	28 / 209 (13.40%)
occurrences (all)	8	2	53
Catheter site pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	6 / 209 (2.87%)
occurrences (all)	1	1	6
Face oedema			

subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	9 / 38 (23.68%)	8 / 19 (42.11%)	109 / 209 (52.15%)
occurrences (all)	12	9	160
Feeling abnormal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Feeling cold			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	1	0	2
Gait disturbance			
subjects affected / exposed	0 / 38 (0.00%)	3 / 19 (15.79%)	8 / 209 (3.83%)
occurrences (all)	0	4	9
Influenza like illness			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	5 / 209 (2.39%)
occurrences (all)	1	1	6
Malaise			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	5 / 209 (2.39%)
occurrences (all)	0	1	5
Non-cardiac chest pain			
subjects affected / exposed	3 / 38 (7.89%)	1 / 19 (5.26%)	9 / 209 (4.31%)
occurrences (all)	3	1	10
Oedema peripheral			
subjects affected / exposed	4 / 38 (10.53%)	1 / 19 (5.26%)	40 / 209 (19.14%)
occurrences (all)	4	3	48
Pain			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	7 / 209 (3.35%)
occurrences (all)	1	1	7
Pyrexia			
subjects affected / exposed	4 / 38 (10.53%)	2 / 19 (10.53%)	19 / 209 (9.09%)
occurrences (all)	5	2	27
Temperature intolerance			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences (all)	0	1	2
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	2	0	2
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	9 / 38 (23.68%)	3 / 19 (15.79%)	62 / 209 (29.67%)
occurrences (all)	9	3	79
Dysphonia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 19 (5.26%)	4 / 209 (1.91%)
occurrences (all)	2	1	4
Dyspnoea			
subjects affected / exposed	10 / 38 (26.32%)	2 / 19 (10.53%)	51 / 209 (24.40%)
occurrences (all)	11	2	77
Dyspnoea exertional			
subjects affected / exposed	3 / 38 (7.89%)	0 / 19 (0.00%)	12 / 209 (5.74%)
occurrences (all)	3	0	16
Epistaxis			
subjects affected / exposed	2 / 38 (5.26%)	2 / 19 (10.53%)	7 / 209 (3.35%)
occurrences (all)	2	2	10
Haemoptysis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	3 / 209 (1.44%)
occurrences (all)	1	1	3
Hypoxia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	6 / 209 (2.87%)
occurrences (all)	0	2	6
Nasal congestion			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	6 / 209 (2.87%)
occurrences (all)	1	1	6
Oropharyngeal pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	8 / 209 (3.83%)
occurrences (all)	2	0	8
Paranasal sinus hypersecretion			

subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences (all)	2	0	1
Pleural effusion			
subjects affected / exposed	2 / 38 (5.26%)	2 / 19 (10.53%)	6 / 209 (2.87%)
occurrences (all)	2	2	7
Pleuritic pain			
subjects affected / exposed	3 / 38 (7.89%)	2 / 19 (10.53%)	1 / 209 (0.48%)
occurrences (all)	3	2	1
Pneumonitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	1	1	3
Pulmonary embolism			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	5 / 209 (2.39%)
occurrences (all)	0	1	6
Pulmonary hypertension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Respiratory distress			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	0	0	2
Respiratory failure			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Throat tightness			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Wheezing			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	4 / 209 (1.91%)
occurrences (all)	1	1	5
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	19 / 209 (9.09%)
occurrences (all)	0	2	19
Confusional state			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	8 / 209 (3.83%)
occurrences (all)	0	0	8

Depression			
subjects affected / exposed	3 / 38 (7.89%)	3 / 19 (15.79%)	8 / 209 (3.83%)
occurrences (all)	3	3	8
Insomnia			
subjects affected / exposed	4 / 38 (10.53%)	2 / 19 (10.53%)	19 / 209 (9.09%)
occurrences (all)	4	2	21
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 38 (7.89%)	3 / 19 (15.79%)	19 / 209 (9.09%)
occurrences (all)	3	4	25
Amylase increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 38 (10.53%)	4 / 19 (21.05%)	21 / 209 (10.05%)
occurrences (all)	4	5	38
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 38 (10.53%)	1 / 19 (5.26%)	13 / 209 (6.22%)
occurrences (all)	5	1	21
Blood bilirubin increased			
subjects affected / exposed	0 / 38 (0.00%)	4 / 19 (21.05%)	16 / 209 (7.66%)
occurrences (all)	0	11	34
Blood creatinine increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	13 / 209 (6.22%)
occurrences (all)	0	4	19
Blood glucose increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	4 / 209 (1.91%)
occurrences (all)	1	1	5
Blood phosphorus decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	0	0	2
Blood urine present			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 38 (0.00%)	3 / 19 (15.79%)	61 / 209 (29.19%)
occurrences (all)	0	5	135
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences (all)	0	1	2
Insulin C-peptide increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences (all)	0	1	2
Lipase increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	3 / 209 (1.44%)
occurrences (all)	0	0	6
Lymphocyte count decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	12 / 209 (5.74%)
occurrences (all)	0	0	23
Neutrophil count increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences (all)	0	1	3
Platelet count decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	20 / 209 (9.57%)
occurrences (all)	0	0	30
QRS axis abnormal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	5 / 209 (2.39%)
occurrences (all)	0	2	7
Weight decreased			
subjects affected / exposed	4 / 38 (10.53%)	4 / 19 (21.05%)	59 / 209 (28.23%)
occurrences (all)	6	6	69
White blood cell count decreased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	19 / 209 (9.09%)
occurrences (all)	1	0	43
Injury, poisoning and procedural			

complications			
Contusion			
subjects affected / exposed	0 / 38 (0.00%)	3 / 19 (15.79%)	14 / 209 (6.70%)
occurrences (all)	0	3	14
Fall			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	9 / 209 (4.31%)
occurrences (all)	0	2	10
Femoral neck fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Hip fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	10 / 209 (4.78%)
occurrences (all)	1	1	12
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Amnesia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	4 / 209 (1.91%)
occurrences (all)	1	1	4
Ataxia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Balance disorder			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	3
Dizziness			
subjects affected / exposed	4 / 38 (10.53%)	4 / 19 (21.05%)	25 / 209 (11.96%)
occurrences (all)	4	4	32
Dysarthria			

subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	0 / 209 (0.00%)
occurrences (all)	0	2	0
Dysgeusia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 19 (10.53%)	17 / 209 (8.13%)
occurrences (all)	1	2	18
Headache			
subjects affected / exposed	6 / 38 (15.79%)	5 / 19 (26.32%)	57 / 209 (27.27%)
occurrences (all)	7	6	72
Hemiparesis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	3 / 209 (1.44%)
occurrences (all)	0	1	3
Hypoaesthesia			
subjects affected / exposed	1 / 38 (2.63%)	3 / 19 (15.79%)	5 / 209 (2.39%)
occurrences (all)	1	3	6
Neuropathy peripheral			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	5 / 209 (2.39%)
occurrences (all)	1	1	6
Paraesthesia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	10 / 209 (4.78%)
occurrences (all)	3	0	10
Restless legs syndrome			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences (all)	0	0	1
Tension headache			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 38 (2.63%)	3 / 19 (15.79%)	7 / 209 (3.35%)
occurrences (all)	1	3	7
Vocal cord paralysis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	5 / 38 (13.16%)	3 / 19 (15.79%)	47 / 209 (22.49%)
occurrences (all)	5	5	91
Increased tendency to bruise			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	1 / 209 (0.48%)
occurrences (all)	0	2	1
Leukocytosis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	3 / 209 (1.44%)
occurrences (all)	2	0	3
Leukopenia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	8 / 209 (3.83%)
occurrences (all)	1	0	9
Lymphopenia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	9 / 209 (4.31%)
occurrences (all)	0	1	14
Neutropenia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 19 (0.00%)	10 / 209 (4.78%)
occurrences (all)	2	0	15
Thrombocytopenia			
subjects affected / exposed	3 / 38 (7.89%)	3 / 19 (15.79%)	21 / 209 (10.05%)
occurrences (all)	3	8	33
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Dysacusis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	16 / 209 (7.66%)
occurrences (all)	0	0	21
Diplopia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences (all)	0	1	2
Dry eye			

subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	4 / 209 (1.91%)
occurrences (all)	1	1	4
Lacrimation increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	13 / 209 (6.22%)
occurrences (all)	1	1	13
Visual acuity reduced			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	4 / 209 (1.91%)
occurrences (all)	1	1	4
Visual impairment			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	5 / 209 (2.39%)
occurrences (all)	0	0	5
Vitreous floaters			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	3 / 209 (1.44%)
occurrences (all)	0	1	3
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	8 / 209 (3.83%)
occurrences (all)	0	1	8
Abdominal pain			
subjects affected / exposed	3 / 38 (7.89%)	4 / 19 (21.05%)	25 / 209 (11.96%)
occurrences (all)	4	4	38
Abdominal pain upper			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	15 / 209 (7.18%)
occurrences (all)	2	0	15
Constipation			
subjects affected / exposed	9 / 38 (23.68%)	2 / 19 (10.53%)	42 / 209 (20.10%)
occurrences (all)	11	2	56
Diarrhoea			
subjects affected / exposed	8 / 38 (21.05%)	11 / 19 (57.89%)	121 / 209 (57.89%)
occurrences (all)	14	14	193
Dry mouth			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	26 / 209 (12.44%)
occurrences (all)	3	0	35

Dyspepsia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 19 (10.53%)	7 / 209 (3.35%)
occurrences (all)	3	2	7
Flatulence			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	3 / 209 (1.44%)
occurrences (all)	0	1	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	22 / 209 (10.53%)
occurrences (all)	0	4	25
Gingival bleeding			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences (all)	0	1	2
Ileus			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	1 / 209 (0.48%)
occurrences (all)	0	2	1
Mouth ulceration			
subjects affected / exposed	3 / 38 (7.89%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences (all)	3	0	1
Nausea			
subjects affected / exposed	14 / 38 (36.84%)	11 / 19 (57.89%)	95 / 209 (45.45%)
occurrences (all)	23	18	143
Pancreatitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	5 / 209 (2.39%)
occurrences (all)	0	0	9
Retching			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	3 / 209 (1.44%)
occurrences (all)	0	1	3
Toothache			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	1 / 209 (0.48%)
occurrences (all)	2	0	1
Vomiting			
subjects affected / exposed	9 / 38 (23.68%)	6 / 19 (31.58%)	65 / 209 (31.10%)
occurrences (all)	16	10	93
Hepatobiliary disorders			
Hyperbilirubinaemia			

subjects affected / exposed	2 / 38 (5.26%)	1 / 19 (5.26%)	6 / 209 (2.87%)
occurrences (all)	2	1	8
Jaundice			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	13 / 209 (6.22%)
occurrences (all)	2	0	14
Dry skin			
subjects affected / exposed	1 / 38 (2.63%)	3 / 19 (15.79%)	14 / 209 (6.70%)
occurrences (all)	1	3	17
Photosensitivity reaction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	5 / 209 (2.39%)
occurrences (all)	1	1	5
Rash			
subjects affected / exposed	3 / 38 (7.89%)	2 / 19 (10.53%)	17 / 209 (8.13%)
occurrences (all)	3	3	18
Rash morbilliform			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Skin erosion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	8 / 209 (3.83%)
occurrences (all)	1	1	8
Renal impairment			

subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Urge incontinence			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Urinary tract disorder			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 38 (13.16%)	3 / 19 (15.79%)	23 / 209 (11.00%)
occurrences (all)	10	4	28
Back pain			
subjects affected / exposed	6 / 38 (15.79%)	3 / 19 (15.79%)	26 / 209 (12.44%)
occurrences (all)	8	4	32
Bone pain			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	4 / 209 (1.91%)
occurrences (all)	0	2	4
Flank pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	5 / 209 (2.39%)
occurrences (all)	0	1	5
Joint swelling			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	4 / 38 (10.53%)	6 / 19 (31.58%)	57 / 209 (27.27%)
occurrences (all)	7	8	74
Muscular weakness			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	9 / 209 (4.31%)
occurrences (all)	0	2	10
Musculoskeletal chest pain			
subjects affected / exposed	3 / 38 (7.89%)	2 / 19 (10.53%)	12 / 209 (5.74%)
occurrences (all)	3	4	14
Musculoskeletal discomfort			

subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	3	0	2
Musculoskeletal pain			
subjects affected / exposed	8 / 38 (21.05%)	1 / 19 (5.26%)	20 / 209 (9.57%)
occurrences (all)	8	1	21
Myalgia			
subjects affected / exposed	5 / 38 (13.16%)	4 / 19 (21.05%)	23 / 209 (11.00%)
occurrences (all)	7	5	33
Pain in extremity			
subjects affected / exposed	3 / 38 (7.89%)	0 / 19 (0.00%)	14 / 209 (6.70%)
occurrences (all)	3	0	17
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	0 / 209 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	3 / 209 (1.44%)
occurrences (all)	0	1	3
Eye infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	6 / 209 (2.87%)
occurrences (all)	1	1	6
Pneumonia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 19 (5.26%)	12 / 209 (5.74%)
occurrences (all)	3	1	12

Rhinitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	1 / 209 (0.48%)
occurrences (all)	0	2	1
Sinusitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	6 / 209 (2.87%)
occurrences (all)	0	1	6
Tooth infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	2 / 209 (0.96%)
occurrences (all)	0	1	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 38 (7.89%)	2 / 19 (10.53%)	23 / 209 (11.00%)
occurrences (all)	4	2	26
Urinary tract infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	27 / 209 (12.92%)
occurrences (all)	1	3	39
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	1 / 209 (0.48%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 38 (23.68%)	10 / 19 (52.63%)	80 / 209 (38.28%)
occurrences (all)	9	14	114
Dehydration			
subjects affected / exposed	3 / 38 (7.89%)	4 / 19 (21.05%)	21 / 209 (10.05%)
occurrences (all)	3	4	24
Glucose tolerance impaired			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	6 / 209 (2.87%)
occurrences (all)	0	2	6
Gout			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	0 / 209 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	4 / 38 (10.53%)	10 / 19 (52.63%)	113 / 209 (54.07%)
occurrences (all)	7	15	294
Hyperkalaemia			

subjects affected / exposed	1 / 38 (2.63%)	1 / 19 (5.26%)	7 / 209 (3.35%)
occurrences (all)	1	1	9
Hypoalbuminaemia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 19 (10.53%)	18 / 209 (8.61%)
occurrences (all)	3	3	21
Hypocalcaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	6 / 209 (2.87%)
occurrences (all)	0	1	7
Hypoglycaemia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 19 (0.00%)	2 / 209 (0.96%)
occurrences (all)	2	0	2
Hypokalaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 19 (5.26%)	27 / 209 (12.92%)
occurrences (all)	0	2	34
Hypomagnesaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 19 (0.00%)	25 / 209 (11.96%)
occurrences (all)	0	0	32
Hyponatraemia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 19 (10.53%)	25 / 209 (11.96%)
occurrences (all)	0	2	35

Non-serious adverse events	Rociletinib 625 mg BID HBr Tablets	Rociletinib 750 mg BID HBr Tablets	Rociletinib 1000 mg BID HBr Tablets
Total subjects affected by non-serious adverse events			
subjects affected / exposed	244 / 245 (99.59%)	95 / 95 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	38 / 245 (15.51%)	26 / 95 (27.37%)	1 / 6 (16.67%)
occurrences (all)	43	34	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	11 / 245 (4.49%)	7 / 95 (7.37%)	0 / 6 (0.00%)
occurrences (all)	20	9	0
Hypotension			

subjects affected / exposed	9 / 245 (3.67%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	12	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	34 / 245 (13.88%)	17 / 95 (17.89%)	1 / 6 (16.67%)
occurrences (all)	52	24	1
Catheter site pain			
subjects affected / exposed	3 / 245 (1.22%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Chills			
subjects affected / exposed	9 / 245 (3.67%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	12	1	0
Face oedema			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	124 / 245 (50.61%)	47 / 95 (49.47%)	3 / 6 (50.00%)
occurrences (all)	190	90	6
Feeling abnormal			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Feeling cold			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Gait disturbance			
subjects affected / exposed	10 / 245 (4.08%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	11	1	0
Influenza like illness			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Malaise			
subjects affected / exposed	3 / 245 (1.22%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Non-cardiac chest pain			

subjects affected / exposed	18 / 245 (7.35%)	4 / 95 (4.21%)	0 / 6 (0.00%)
occurrences (all)	24	4	0
Oedema peripheral			
subjects affected / exposed	31 / 245 (12.65%)	14 / 95 (14.74%)	0 / 6 (0.00%)
occurrences (all)	35	19	0
Pain			
subjects affected / exposed	8 / 245 (3.27%)	6 / 95 (6.32%)	0 / 6 (0.00%)
occurrences (all)	8	6	0
Pyrexia			
subjects affected / exposed	27 / 245 (11.02%)	7 / 95 (7.37%)	0 / 6 (0.00%)
occurrences (all)	36	7	0
Temperature intolerance			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 245 (0.41%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	59 / 245 (24.08%)	15 / 95 (15.79%)	1 / 6 (16.67%)
occurrences (all)	72	15	1
Dysphonia			
subjects affected / exposed	6 / 245 (2.45%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	8	2	0
Dyspnoea			
subjects affected / exposed	65 / 245 (26.53%)	20 / 95 (21.05%)	2 / 6 (33.33%)
occurrences (all)	89	29	2
Dyspnoea exertional			
subjects affected / exposed	9 / 245 (3.67%)	7 / 95 (7.37%)	0 / 6 (0.00%)
occurrences (all)	10	7	0
Epistaxis			

subjects affected / exposed	12 / 245 (4.90%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	14	2	0
Haemoptysis			
subjects affected / exposed	12 / 245 (4.90%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences (all)	17	1	1
Hypoxia			
subjects affected / exposed	7 / 245 (2.86%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Nasal congestion			
subjects affected / exposed	7 / 245 (2.86%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	8	2	0
Oropharyngeal pain			
subjects affected / exposed	7 / 245 (2.86%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	7	1	0
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	13 / 245 (5.31%)	5 / 95 (5.26%)	1 / 6 (16.67%)
occurrences (all)	17	7	1
Pleuritic pain			
subjects affected / exposed	4 / 245 (1.63%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
Pneumonitis			
subjects affected / exposed	7 / 245 (2.86%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences (all)	12	3	0
Pulmonary embolism			
subjects affected / exposed	6 / 245 (2.45%)	2 / 95 (2.11%)	1 / 6 (16.67%)
occurrences (all)	8	2	1
Pulmonary hypertension			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Respiratory failure			

subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Throat tightness			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	3 / 245 (1.22%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	20 / 245 (8.16%)	8 / 95 (8.42%)	1 / 6 (16.67%)
occurrences (all)	23	8	1
Confusional state			
subjects affected / exposed	13 / 245 (5.31%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences (all)	15	4	0
Depression			
subjects affected / exposed	12 / 245 (4.90%)	4 / 95 (4.21%)	1 / 6 (16.67%)
occurrences (all)	12	4	1
Insomnia			
subjects affected / exposed	31 / 245 (12.65%)	8 / 95 (8.42%)	0 / 6 (0.00%)
occurrences (all)	33	10	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 245 (10.61%)	8 / 95 (8.42%)	0 / 6 (0.00%)
occurrences (all)	48	12	0
Amylase increased			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	26 / 245 (10.61%)	10 / 95 (10.53%)	0 / 6 (0.00%)
occurrences (all)	40	11	0
Blood alkaline phosphatase increased			
subjects affected / exposed	16 / 245 (6.53%)	7 / 95 (7.37%)	1 / 6 (16.67%)
occurrences (all)	25	8	1
Blood bilirubin increased			

subjects affected / exposed	15 / 245 (6.12%)	13 / 95 (13.68%)	1 / 6 (16.67%)
occurrences (all)	24	20	1
Blood creatinine increased			
subjects affected / exposed	20 / 245 (8.16%)	7 / 95 (7.37%)	1 / 6 (16.67%)
occurrences (all)	38	12	3
Blood glucose increased			
subjects affected / exposed	9 / 245 (3.67%)	7 / 95 (7.37%)	2 / 6 (33.33%)
occurrences (all)	12	15	2
Blood phosphorus decreased			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Blood urine present			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	77 / 245 (31.43%)	33 / 95 (34.74%)	3 / 6 (50.00%)
occurrences (all)	185	65	3
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Glycosylated haemoglobin increased			
subjects affected / exposed	12 / 245 (4.90%)	2 / 95 (2.11%)	1 / 6 (16.67%)
occurrences (all)	12	2	1
Insulin C-peptide increased			
subjects affected / exposed	11 / 245 (4.49%)	5 / 95 (5.26%)	0 / 6 (0.00%)
occurrences (all)	11	5	0
Lipase increased			
subjects affected / exposed	2 / 245 (0.82%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences (all)	2	1	2
Lymphocyte count decreased			
subjects affected / exposed	8 / 245 (3.27%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	17	2	0
Neutrophil count increased			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Platelet count decreased			

subjects affected / exposed	17 / 245 (6.94%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences (all)	37	6	0
QRS axis abnormal			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	4 / 245 (1.63%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences (all)	4	1	1
Weight decreased			
subjects affected / exposed	63 / 245 (25.71%)	39 / 95 (41.05%)	2 / 6 (33.33%)
occurrences (all)	87	50	3
White blood cell count decreased			
subjects affected / exposed	20 / 245 (8.16%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	51	7	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	14 / 245 (5.71%)	4 / 95 (4.21%)	0 / 6 (0.00%)
occurrences (all)	14	4	0
Fall			
subjects affected / exposed	8 / 245 (3.27%)	4 / 95 (4.21%)	0 / 6 (0.00%)
occurrences (all)	12	4	0
Femoral neck fracture			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hip fracture			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 245 (0.41%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Amnesia			

subjects affected / exposed	2 / 245 (0.82%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Ataxia			
subjects affected / exposed	3 / 245 (1.22%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Balance disorder			
subjects affected / exposed	3 / 245 (1.22%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	1
Disturbance in attention			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	41 / 245 (16.73%)	14 / 95 (14.74%)	1 / 6 (16.67%)
occurrences (all)	50	14	2
Dysarthria			
subjects affected / exposed	0 / 245 (0.00%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Dysgeusia			
subjects affected / exposed	16 / 245 (6.53%)	5 / 95 (5.26%)	0 / 6 (0.00%)
occurrences (all)	18	5	0
Headache			
subjects affected / exposed	57 / 245 (23.27%)	20 / 95 (21.05%)	1 / 6 (16.67%)
occurrences (all)	73	26	1
Hemiparesis			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Hypoaesthesia			
subjects affected / exposed	6 / 245 (2.45%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	7	4	0
Neuropathy peripheral			
subjects affected / exposed	9 / 245 (3.67%)	4 / 95 (4.21%)	0 / 6 (0.00%)
occurrences (all)	9	5	0
Paraesthesia			
subjects affected / exposed	17 / 245 (6.94%)	4 / 95 (4.21%)	0 / 6 (0.00%)
occurrences (all)	18	5	0
Restless legs syndrome			

subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	6 / 245 (2.45%)	5 / 95 (5.26%)	0 / 6 (0.00%)
occurrences (all)	6	6	0
Tension headache			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	7 / 245 (2.86%)	4 / 95 (4.21%)	1 / 6 (16.67%)
occurrences (all)	8	5	2
Vocal cord paralysis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	74 / 245 (30.20%)	19 / 95 (20.00%)	1 / 6 (16.67%)
occurrences (all)	131	41	1
Increased tendency to bruise			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	3 / 245 (1.22%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Leukopenia			
subjects affected / exposed	8 / 245 (3.27%)	6 / 95 (6.32%)	0 / 6 (0.00%)
occurrences (all)	10	6	0
Lymphopenia			
subjects affected / exposed	9 / 245 (3.67%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	19	0	0
Neutropenia			
subjects affected / exposed	11 / 245 (4.49%)	7 / 95 (7.37%)	0 / 6 (0.00%)
occurrences (all)	14	11	0
Thrombocytopenia			
subjects affected / exposed	19 / 245 (7.76%)	17 / 95 (17.89%)	0 / 6 (0.00%)
occurrences (all)	30	41	0

Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysacusis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	29 / 245 (11.84%)	17 / 95 (17.89%)	2 / 6 (33.33%)
occurrences (all)	34	21	3
Diplopia			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	9 / 245 (3.67%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	9	0	0
Lacrimation increased			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Vision blurred			
subjects affected / exposed	18 / 245 (7.35%)	13 / 95 (13.68%)	0 / 6 (0.00%)
occurrences (all)	21	15	0
Visual acuity reduced			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Visual impairment			
subjects affected / exposed	5 / 245 (2.04%)	3 / 95 (3.16%)	1 / 6 (16.67%)
occurrences (all)	5	3	1
Vitreous floaters			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 245 (3.27%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences (all)	8	4	0
Abdominal pain			

subjects affected / exposed	39 / 245 (15.92%)	17 / 95 (17.89%)	0 / 6 (0.00%)
occurrences (all)	51	21	0
Abdominal pain upper			
subjects affected / exposed	18 / 245 (7.35%)	11 / 95 (11.58%)	2 / 6 (33.33%)
occurrences (all)	23	14	2
Constipation			
subjects affected / exposed	94 / 245 (38.37%)	26 / 95 (27.37%)	2 / 6 (33.33%)
occurrences (all)	117	31	2
Diarrhoea			
subjects affected / exposed	146 / 245 (59.59%)	54 / 95 (56.84%)	3 / 6 (50.00%)
occurrences (all)	292	82	4
Dry mouth			
subjects affected / exposed	22 / 245 (8.98%)	16 / 95 (16.84%)	0 / 6 (0.00%)
occurrences (all)	23	17	0
Dyspepsia			
subjects affected / exposed	6 / 245 (2.45%)	5 / 95 (5.26%)	1 / 6 (16.67%)
occurrences (all)	6	5	1
Flatulence			
subjects affected / exposed	3 / 245 (1.22%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	26 / 245 (10.61%)	12 / 95 (12.63%)	0 / 6 (0.00%)
occurrences (all)	31	14	0
Gingival bleeding			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ileus			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	3 / 245 (1.22%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Nausea			
subjects affected / exposed	138 / 245 (56.33%)	51 / 95 (53.68%)	3 / 6 (50.00%)
occurrences (all)	218	78	6
Pancreatitis			

subjects affected / exposed	5 / 245 (2.04%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences (all)	5	2	2
Retching			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	2 / 245 (0.82%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Vomiting			
subjects affected / exposed	82 / 245 (33.47%)	32 / 95 (33.68%)	2 / 6 (33.33%)
occurrences (all)	135	46	2
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	6 / 245 (2.45%)	5 / 95 (5.26%)	0 / 6 (0.00%)
occurrences (all)	8	12	0
Jaundice			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 245 (3.67%)	11 / 95 (11.58%)	0 / 6 (0.00%)
occurrences (all)	10	15	0
Dry skin			
subjects affected / exposed	18 / 245 (7.35%)	5 / 95 (5.26%)	1 / 6 (16.67%)
occurrences (all)	18	5	1
Photosensitivity reaction			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	12 / 245 (4.90%)	4 / 95 (4.21%)	0 / 6 (0.00%)
occurrences (all)	15	4	0
Rash			
subjects affected / exposed	13 / 245 (5.31%)	12 / 95 (12.63%)	0 / 6 (0.00%)
occurrences (all)	18	12	0
Rash morbilliform			

subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin erosion			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	2 / 245 (0.82%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Pollakiuria			
subjects affected / exposed	12 / 245 (4.90%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	17	1	0
Renal impairment			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urge incontinence			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract disorder			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 245 (12.65%)	13 / 95 (13.68%)	0 / 6 (0.00%)
occurrences (all)	35	14	0
Back pain			
subjects affected / exposed	43 / 245 (17.55%)	15 / 95 (15.79%)	0 / 6 (0.00%)
occurrences (all)	48	16	0
Bone pain			
subjects affected / exposed	4 / 245 (1.63%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Flank pain			
subjects affected / exposed	4 / 245 (1.63%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences (all)	5	3	0
Joint swelling			

subjects affected / exposed	1 / 245 (0.41%)	3 / 95 (3.16%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Muscle spasms			
subjects affected / exposed	71 / 245 (28.98%)	27 / 95 (28.42%)	2 / 6 (33.33%)
occurrences (all)	111	35	3
Muscular weakness			
subjects affected / exposed	12 / 245 (4.90%)	5 / 95 (5.26%)	0 / 6 (0.00%)
occurrences (all)	12	6	0
Musculoskeletal chest pain			
subjects affected / exposed	21 / 245 (8.57%)	13 / 95 (13.68%)	1 / 6 (16.67%)
occurrences (all)	27	14	1
Musculoskeletal discomfort			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	22 / 245 (8.98%)	10 / 95 (10.53%)	0 / 6 (0.00%)
occurrences (all)	23	11	0
Myalgia			
subjects affected / exposed	16 / 245 (6.53%)	10 / 95 (10.53%)	1 / 6 (16.67%)
occurrences (all)	18	10	1
Pain in extremity			
subjects affected / exposed	23 / 245 (9.39%)	5 / 95 (5.26%)	0 / 6 (0.00%)
occurrences (all)	31	6	0
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	5 / 245 (2.04%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
Clostridium difficile infection			
subjects affected / exposed	4 / 245 (1.63%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	5	0	1
Cystitis			
subjects affected / exposed	1 / 245 (0.41%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Eye infection			
subjects affected / exposed	0 / 245 (0.00%)	1 / 95 (1.05%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Folliculitis			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	9 / 245 (3.67%)	0 / 95 (0.00%)	0 / 6 (0.00%)
occurrences (all)	12	0	0
Pneumonia			
subjects affected / exposed	15 / 245 (6.12%)	11 / 95 (11.58%)	2 / 6 (33.33%)
occurrences (all)	18	15	3
Rhinitis			
subjects affected / exposed	1 / 245 (0.41%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	9 / 245 (3.67%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	11	1	0
Tooth infection			
subjects affected / exposed	6 / 245 (2.45%)	1 / 95 (1.05%)	0 / 6 (0.00%)
occurrences (all)	6	1	0
Upper respiratory tract infection			
subjects affected / exposed	16 / 245 (6.53%)	14 / 95 (14.74%)	1 / 6 (16.67%)
occurrences (all)	19	14	1
Urinary tract infection			
subjects affected / exposed	25 / 245 (10.20%)	18 / 95 (18.95%)	0 / 6 (0.00%)
occurrences (all)	38	28	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 245 (0.41%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	92 / 245 (37.55%)	43 / 95 (45.26%)	4 / 6 (66.67%)
occurrences (all)	134	59	4
Dehydration			

subjects affected / exposed	30 / 245 (12.24%)	12 / 95 (12.63%)	0 / 6 (0.00%)
occurrences (all)	36	16	0
Glucose tolerance impaired			
subjects affected / exposed	9 / 245 (3.67%)	11 / 95 (11.58%)	0 / 6 (0.00%)
occurrences (all)	11	16	0
Gout			
subjects affected / exposed	0 / 245 (0.00%)	0 / 95 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	147 / 245 (60.00%)	56 / 95 (58.95%)	3 / 6 (50.00%)
occurrences (all)	431	134	6
Hyperkalaemia			
subjects affected / exposed	6 / 245 (2.45%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Hypoalbuminaemia			
subjects affected / exposed	22 / 245 (8.98%)	3 / 95 (3.16%)	0 / 6 (0.00%)
occurrences (all)	31	9	0
Hypocalcaemia			
subjects affected / exposed	11 / 245 (4.49%)	2 / 95 (2.11%)	0 / 6 (0.00%)
occurrences (all)	14	3	0
Hypoglycaemia			
subjects affected / exposed	8 / 245 (3.27%)	6 / 95 (6.32%)	0 / 6 (0.00%)
occurrences (all)	8	7	0
Hypokalaemia			
subjects affected / exposed	44 / 245 (17.96%)	14 / 95 (14.74%)	1 / 6 (16.67%)
occurrences (all)	58	16	1
Hypomagnesaemia			
subjects affected / exposed	30 / 245 (12.24%)	10 / 95 (10.53%)	2 / 6 (33.33%)
occurrences (all)	40	13	2
Hyponatraemia			
subjects affected / exposed	24 / 245 (9.80%)	8 / 95 (8.42%)	1 / 6 (16.67%)
occurrences (all)	28	14	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2012	Patient enrollment began into the Phase 1 portion of the study. Dose escalation was initiated at 150 mg QD with the FB rociletinib formulation.
04 October 2012	Patients were enrolled at approximately 6 sites for Phase 1 and approximately 12 to 15 sites for Phase 2.
08 July 2013	The rociletinib 125 mg HBr tablet was introduced under this amendment and a CRM replaced the 3 + 3 dose escalation schema. Enrollment was increased to approximately 170 patients in both phases at up to 8 investigative sites for Phase 1 and 12 to 15 for Phase 2. An additional Phase 2 cohort was added, and Cohorts A and B were defined.
10 December 2013	A higher strength 250 mg rociletinib HBr tablet was made available in addition to the 125 mg strength in the previous amendment. An initial RP2D of 750 mg BID was selected for Phase 2 and enrollment into Phase 2 was initiated under this amendment (starting in January 2014). Inclusion and exclusion criteria were modified, and minor adjustments were made to the sample size and number of study sites and regions to reflect the current status of the study (up to 22 investigative sites for Phase 2). Fasting glucose and hemoglobin A1c were added as clinical laboratory investigation, and guidance for management of rociletinib-related hyperglycemia was provided.
17 April 2014	The total number of patients increased from 172 to approximately 600 (Phase 1: N≈110; Phase 2: N≈490). The number of investigative sites for Phase 2 was increased to approximately 50 sites to accommodate the increase in patient number. The study now had 80% power to detect a 20% difference in ORR between 2 dose groups at the 10% significance level. Formal safety data reviews were performed following the enrollment of every 50 patients, and no less frequently than every quarter. For Phase 2, the primary endpoints of ORR and DOR were specified to be assessed by the investigator, and additional secondary endpoints of OS and DCR were added. Cohort C was added to Phase 2, and rociletinib HBr tablet dose levels of 500 mg BID and 625 mg BID were added to Cohorts A and B in order to evaluate dose response and tolerability in more detail. Patients were no longer to be enrolled at a starting dose of 750 mg BID. Guidelines for management of QT prolongation and hyperglycemia were updated based on identification of these events as key safety signals following completion of the dose escalation portion of Phase 1 in January 2014.
07 August 2014	This amendment allowed the sponsor to enroll the RP2D of 625 mg BID before the 500 mg BID dose in order to increase experience with the RP2D to support the ongoing Phase 2 and Phase 3 rociletinib programs and to increase the total number of patients by approximately 125 patients in Cohort A, for a total of approximately 715 patients (Phase 1 N≈110; Phase 2 N≈605).
03 August 2016	Discontinuation of the rociletinib clinical development program prompted the introduction of a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that would no longer be analyzed or required for regulatory purposes, while maintaining an appropriate level of safety monitoring. A detailed description of the study design and Schedule of Assessments is provided in the Protocol Amendment 8. Through Protocol Amendment 7, response was determined by both investigator assessment (primary endpoint) and IRR (secondary endpoint). Starting in Amendment 8 (Extension Phase), tumor scans were only interpreted locally by the investigator for final tumor response evaluation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 May 2016	Enrollment to the trial ended due to a corporate decision to suspend the development of rociletinib. Patients who were in screening as of 05 May 2016 could enroll on or before 12 May 2016 if they met eligibility requirements. As of that date, a total of 612 patients had enrolled in Study CO-1686-008, with 50 active patients; 42 sites had screened at least 1 patient, and 29 of these sites had enrolled at least 1 patient. As of 27 August 2018, there were no patients remaining on study. The last patient on study (Patient 526609) had her last study visit on 16 August 2018 and died on 27 August 2018. Her last dose of rociletinib was on 26 August 2018. All 49 sites were closed, and the database lock was completed on 13 December 2018.	-

Notes:

Limitations and caveats

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

The following endpoints are not reported since they were not analyzed due to early study termination: PK; ORR, DOR, PFS as determined by independent radiology review; OS, DCR, PFS as determined by investigator assessment; all exploratory objectives.

Notes: