Clinical trial results:
A Study of HSP90 Inhibitor AT13387 Alone and in Combination with Crizotinib in the Treatment of Non-small Cell Lung Cancer (NSCLC).

Summary

EudraCT number	2012-001575-37
Trial protocol	ES
Global end of trial date	21 February 2017

Results information

Result version number	v2 (current)
This version publication date	26 July 2018
First version publication date	06 July 2018
Version creation reason	• Correction of full data set Additional clarification is provided.

Trial information

Trial identification

Sponsor protocol code	AT13387-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01712217
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astex Pharmaceuticals, Inc.
Sponsor organisation address	4420 Rosewood Drive, Suite 200, Pleasanton, CA, United States, 94588
Public contact	Dr Harold Keer, Astex Pharmaceuticals Inc., 001 9257190741, Harold.Keer@astx.com
Scientific contact	Dr Harold Keer, Astex Pharmaceuticals Inc., 001 9257190741, Harold.Keer@astx.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A:
To establish the safety and maximum tolerated dose (MTD) of AT13387 when administered in combination with crizotinib.

Part B:
To compare the progression-free survival (PFS) between the administration of single-agent crizotinib and the combination of crizotinib + AT13387 in subjects with NSCLC who will be treated with crizotinib or who were treated with crizotinib and have not yet progressed.

Part C:
To assess the efficacy (Objective Response Rate [ORR] = complete response [CR] + partial response [PR]) of single-agent AT13387 and to assess the efficacy of the addition of AT13387 to crizotinib in subjects who progressed on treatment with crizotinib.

Protection of trial subjects:

Ethical Conduct of the Study:
The study was conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, applicable local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

Subject Information and Consent:
The informed consent forms (ICFs) used for each study centre complied with ICH, the principles enunciated in the Declaration of Helsinki, local regulatory requirements, and ICH GCP guidelines and was approved by the sponsor and the investigator's IRB/IEC. The investigator, or a person delegated by the investigator, explained the medical aspects of the study, including the nature and purpose of the study and the treatment, the procedures involved, and the potential benefits and risks. Other tasks in the informed consent process may have been delegated by the investigator. After having been informed that participation was voluntary and that subjects may withdraw from the study at any time, without prejudice, each subject signed the IRB/IEC-approved ICF prior to undergoing any study specific procedures and enrolment in the study.

Background therapy:

Prior and Concomitant Therapy:
All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the subject were documented on the concomitant medication eCRF and included start and stop dates and indication. Medications taken for a procedure (e.g., biopsy) were also included.

Supportive treatment was provided, according to the institution standards and at the investigator’s discretion. Dexamethasone and/or antihistamines could be given to treat or prevent systemic infusion reactions. Anti-emetics, anti-diarrhoeal agents, etc., were given as needed to treat or prevent gastrointestinal toxicities.

Crizotinib is a moderate inhibitor of cytochrome P3A (CYP3A); however, the potential of significant clinical drug-drug interaction with CYP3A substrates is unlikely. The aqueous solubility of crizotinib is pH-dependent, with higher pH resulting in lower solubility. Drugs that elevate gastric pH such as proton pump inhibitors, H2 blockers, or antacids may decrease the solubility and reduce the bioavailability of crizotinib, although no formal studies have been conducted. Crizotinib is an inhibitor of P-glycoprotein (P-gp) in vitro. Therefore, it may have the potential to increase the plasma concentrations of co-administered substrates of P-gp.

Electrocardiogram assessments of crizotinib has revealed 1.3% of subjects with QT corrected by the Fridericia's method (QTcF_ >500 msec, and 3.8% of subjects with QTcF increase from baseline greater than 60 msec. A pharmacokinetic (PK)/pharmacodynamic (PD) analysis suggested a dose-dependent increase in QTcF (Xalkori [crizotinib] prescribing information). Drugs that are known to increase QTc were to be avoided or at least used with caution in subjects treated in this study.

Evidence for comparator:

Rationale for Study of Crizotinib and Onalespib Combination Therapy in ALK+ NSCLC:
With the discovery of ALK gene translocations (and resulting EML4-ALK fusion proteins) in ALK+ NSCLC, research on crizotinib, a multi-targeted inhibitor of tyrosine kinases (including ALK), intensified (Ou, 2011). Crizotinib demonstrated concentration-dependent inhibition of ALK phosphorylation in cell-based assays using tumour cell lines and demonstrated anti-tumour activity in mice bearing tumour xenografts that expressed EML4-ALK fusion proteins (Xalkori [crizotinib] Package Insert 2011).

Crizotinib efficacy was subsequently demonstrated in randomised active-controlled clinical trials in patients with metastatic ALK+NSCLC who had not received prior cancer therapy (n=340; first-line treatment; Study 1) and in patients who had previously received treatment with 1 platinum-based chemotherapy regimen (n=343; second-line treatment; Study 2). In both studies, there was a statistically significant improvement in PFS in the patients treated with crizotinib compared with the control arms (Xalkori [crizotinib] Package Insert 2011). Notably, in the second-line treatment study, the median PFS for the crizotinib cohort was 7.7 months (95% CI, 6.0-8.8), compared with PFS in the chemotherapy (pemetrexed or docetaxel) cohort (3.0 months [95% CI, 2.6-4.3], based on Kaplan-Meier estimation; P=<.001 from stratified log-rank test.

Actual start date of recruitment	04 February 2013
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	Canada: 8
Country: Number of subjects enrolled	Korea, Republic of: 87
Country: Number of subjects enrolled	United States: 85
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	France: 31
Worldwide total number of subjects	220
EEA total number of subjects	40

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)	173
From 65 to 84 years	45
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 52 principal investigators at 52 study centres (28 in the US, 12 in Europe, 4 in Canada, and 8 in South Korea) enrolled subjects in this study.

Dates of first treatment was on 04 February 2013, and last observation was on 21 February 2017.

Pre-assignment

Screening details:

278 subjects were assessed (220 subjects enrolled), 57 subjects excluded & 1 subject was enrolled but withdrawn before treatment. Part A, 32 subjects were enrolled & treated. Part B, 136 subjects were enrolled (133 subjects treated). Part C, 52 subjects were enrolled & treated. Baseline characteristics are provided for the subjects in Part A.

Period 1

Period 1 title	Part A (Dose Escalation)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Arm 1 - Crizotinib 250 mg PO & onalespib IV 150 mg/m2

Arm description: -

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

Dosage and administration details:

250 mg crizotinib by mouth twice daily

Investigational medicinal product name	Onalespib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

150 mg/m2 onalespib by IV infusion once weekly for 3 weeks in every 4-week cycle (on Days 1, 8 and 15 of a 28-day cycle)

Arm title	Part A: Arm 2 - Crizotinib 250 mg PO & onalespib IV 180 mg/m2

Arm description: -

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

Dosage and administration details:

250 mg crizotinib by mouth twice daily

Investigational medicinal product name	Onalespib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

180 mg/m2 onalespib by IV infusion once weekly for 3 weeks in every 4-week cycle (on Days 1, 8 and 15 of a 28-day cycle)

Arm title	Part A: Arm 3- Crizotinib 250mg PO and onalespib IV 220 mg/m2

Arm description: -

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

Dosage and administration details:

250 mg crizotinib by mouth twice daily

Investigational medicinal product name	Onalespib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

220 mg/m2 onalespib by IV infusion once weekly for 3 weeks in every 4-week cycle (on Days 1, 8 and 15 of a 28-day cycle)

Number of subjects in period 1[1]	Part A: Arm 1 - Crizotinib 250 mg PO & onalespib IV 150 mg/m2	Part A: Arm 2 - Crizotinib 250 mg PO & onalespib IV 180 mg/m2	Part A: Arm 3- Crizotinib 250mg PO and onalespib IV 220 mg/m2
Started	8	9	15
Completed	8	9	15

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The study was conducted in 3 parts. Only 1 part can be identified as the baseline period.

Period 2

Period 2 title	Part B Criz. vs Criz.+ Onalespib
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No

Arm title	Part B: Arm 1 - Crizotinib monotherapy (250 mg PO BID)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 250 mg crizotinib by mouth twice daily	
Arm title	Part B: Arm 2-Crizotinib (250mg PO) + onalespib (220 mg/m2 IV)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Onalespib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use
Dosage and administration details: 220 mg/m2 onalespib by IV infusion once weekly for 3 weeks in every 4-week cycle (on Days 1, 8 and 15 of a 28-day cycle)	
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 250 mg crizotinib by mouth twice daily	

Number of subjects in period 2	Part B: Arm 1 - Crizotinib monotherapy (250 mg PO BID)	Part B: Arm 2-Crizotinib (250mg PO) + onalespib (220 mg/m2 IV)
Started	68	68
Completed	55	50
Not completed	13	18
Consent withdrawn by subject	8	13
Did not complete for other reasons	2	4
Lost to follow-up	3	1

Period 3

Period 3 title	Part C Onalespib vs Criz. + Onalespib
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part C: Arm 1- Onalespib monotherapy (260 mg/m2 IV)

Arm description:

Onalespib monotherapy (260 mg/m2 IV)

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

Dosage and administration details:

260 mg/m2 onalespib by IV infusion once weekly for 3 weeks in every 4-week cycle (on Days 1, 8 and 15 of a 28-day cycle)

Arm title	Part C: Arm 2- Crizotinib 250mg + onalespib 220mg/m2

Arm description:

Crizotinib 250mg + onalespib 220mg/m2

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

Dosage and administration details:

250 mg crizotinib by mouth twice daily

Investigational medicinal product name	Onalespib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

220 mg/m2 onalespib by IV infusion once weekly for 3 weeks in every 4-week cycle (on Days 1, 8 and 15 of a 28-day cycle)

Number of subjects in period 3	Part C: Arm 1- Onalespib monotherapy (260 mg/m2 IV)	Part C: Arm 2- Crizotinib 250mg + onalespib 220mg/m2
Started	24	28
Completed	23	25
Not completed	1	3
Consent withdrawn by subject	1	2

Did not complete for other reasons	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Arm 1 - Crizotinib 250 mg PO & onalespib IV 150 mg/m2
Reporting group description: -	
Reporting group title	Part A: Arm 2 - Crizotinib 250 mg PO & onalespib IV 180 mg/m2
Reporting group description: -	
Reporting group title	Part A: Arm 3- Crizotinib 250mg PO and onalespib IV 220 mg/m2
Reporting group description: -	

Reporting group values	Part A: Arm 1 - Crizotinib 250 mg PO & onalespib IV 150 mg/m2	Part A: Arm 2 - Crizotinib 250 mg PO & onalespib IV 180 mg/m2	Part A: Arm 3- Crizotinib 250mg PO and onalespib IV 220 mg/m2
Number of subjects	8	9	15
Age categorical Units: Subjects			
Part A	8	9	15
Age continuous Units: years			
arithmetic mean	51.9	56.7	58.5
standard deviation	± 10.4	± 13.2	± 11.2
Gender categorical Units: Subjects			
Female	4	6	8
Male	4	3	7

Reporting group values	Total		
Number of subjects	32		
Age categorical Units: Subjects			
Part A	32		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	18		
Male	14		

End points

End points reporting groups

Reporting group title	Part A: Arm 1 - Crizotinib 250 mg PO & onalespib IV 150 mg/m2
Reporting group description: -	
Reporting group title	Part A: Arm 2 - Crizotinib 250 mg PO & onalespib IV 180 mg/m2
Reporting group description: -	
Reporting group title	Part A: Arm 3- Crizotinib 250mg PO and onalespib IV 220 mg/m2
Reporting group description: -	
Reporting group title	Part B: Arm 1 - Crizotinib monotherapy (250 mg PO BID)
Reporting group description: -	
Reporting group title	Part B: Arm 2-Crizotinib (250mg PO) + onalespib (220 mg/m2 IV)
Reporting group description: -	
Reporting group title	Part C: Arm 1- Onalespib monotherapy (260 mg/m2 IV)
Reporting group description: Onalespib monotherapy (260 mg/m2 IV)	
Reporting group title	Part C: Arm 2- Crizotinib 250mg + onalespib 220mg/m2
Reporting group description: Crizotinib 250mg + onalespib 220mg/m2	

Primary: Part A - The incidence of DLTs when onalespib was administered in combination with crizotinib.

End point title	Part A - The incidence of DLTs when onalespib was administered in combination with crizotinib.[1]

End point description:

Dose-limiting toxicities were defined in the protocol as AEs occurring in Cycle 1 of Part A or any cycle of Parts B and C judged to be related to the study treatment (onalespib or crizotinib) that represent any 1 of the following:

- Grade 4 neutropenia or thrombocytopenia that lasts for more than 1 week or associated with neutropenic fever or bleeding.
- Grade 3 or 4 non-hematologic toxicity, including:

o ≥Grade 3 nausea and vomiting despite maximal anti-emetic treatment and lasting >48 hours,
o ≥Grade 3 diarrhea despite maximal anti-diarrheal treatment and lasting >48 hours, or
o ≥Grade 3 fatigue lasting >3 days.

- Toxicity that results in discontinuation of treatment or ≥4 weeks delay of treatment.

The Data and Safety Review Committee (DSRC) could consider other clinically significant adverse events as dose limiting based on their collective clinical judgment.

No dose-limiting toxicities occurred in Part A of the study.

End point type	Primary

End point timeframe:

Subjects treated once weekly for 3 weeks in a 4-week cycle. Subjects could continue to receive treatment until disease progression, unacceptable toxicity, early termination of the study, or at the discretion of the investigator.

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: Only the descriptive statistics are reported here.

End point values	Part A: Arm 1 - Crizotinib 250 mg PO & onalespib IV 150 mg/m2	Part A: Arm 2 - Crizotinib 250 mg PO & onalespib IV 180 mg/m2	Part A: Arm 3- Crizotinib 250mg PO and onalespib IV 220 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	15	
Units: Subject	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the number of days from randomization date to the earliest of any PFS events, which were defined as follows:
• Disease progression determined by earliest date of progressive disease in the derived evaluation of target lesion, unequivocal progression in the evaluation of nontarget lesion, or appearance of any new lesions.
• Clinical progression reported in the treatment discontinuation CRF page.
• Death from any cause.

Subjects were censored for PFS analysis based as follow, Subjects:
• without a PFS event were censored on the last tumor assessment date.
• who had not baseline or postbaseline disease diagnosis were censored at the date of randomization.
• who received subsequent anticancer therapy or crossed over to the crizotinib monotherapy arm before experiencing an event were right-censored at the date of the last adequate tumor or clinical progression assessment prior to the date of initiation of subsequent therapy or crossover

End point type	Primary

End point timeframe:

Subjects treated once weekly for 3 weeks in a 4-week cycle. Subjects could continue to receive treatment until disease progression, unacceptable toxicity, early termination of the study, or at the discretion of the investigator.

End point values	Part B: Arm 1 - Crizotinib monotherapy (250 mg PO BID)	Part B: Arm 2- Crizotinib (250mg PO) + onalespib (220 mg/m2 IV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	65		
Units: days				
arithmetic mean (confidence interval 95%)	320.0 (239.0 to 392.0)	280.0 (223.0 to 941.0)		

Statistical analyses

Statistical analysis title	Progression-Free Survival - Part B

Statistical analysis description:

PFS was analyzed by Kaplan-Meier procedure for Part B. Median PFS and its 95% CI were provided. Stratified log-rank tests were conducted to compare PFS for treatment groups with stratification factor, duration of prior crizotinib therapy (≤4 months vs >4 months), and 2-sided significance level alpha at 0.05. Hazard ratio and 95% CI were provided using Cox proportional hazard model with treatment group and duration of prior crizotinib therapy as covariates.

Comparison groups	Part B: Arm 1 - Crizotinib monotherapy (250 mg PO BID) v Part B: Arm 2-Crizotinib (250mg PO) + onalespib (220 mg/m2 IV)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3905
Method	Logrank

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[2]

End point description:

Objective Response Rate (ORR) was defined as the proportion of subjects who achieved a best overall objective response of CR (complete response) or PR (partial response). Best overall response in this study was defined as the best response across all time points and was determined once all the data for the subject was known. Best response confirmation of CR or PR was not required. A response of stable disease had to meet the protocol specified minimum time interval of 6 weeks from baseline in order to be considered the best response; a subject lost to follow-up after a first assessment of stable disease would be considered inevaluable. Subjects who did not have disease assessments were considered nonresponders.

End point type	Primary

End point timeframe:

Subjects treated once weekly for 3 weeks in a 4-week cycle. Subjects could continue to receive treatment until disease progression, unacceptable toxicity, early termination of the study, or at the discretion of the investigator.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only the descriptive statistics are reported here.

End point values	Part C: Arm 1- Onalespib monotherapy (260 mg/m2 IV)	Part C: Arm 2- Crizotinib 250mg + onalespib 220mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	27		
Units: percent				
number (confidence interval 95%)	4.3 (0.1 to 21.9)	18.5 (6.3 to 38.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded on scheduled study days and at study follow-up.

Adverse event reporting additional description:

Note: Non-serious Adverse Events (≥5% of Subjects in any group) are reported

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Part A- Arm 1-Crizotinib 250 mg PO and onalespib IV 150 mg/m2
Reporting group description: -	
Reporting group title	Part A- Arm 2-Crizotinib 250 mg PO and onalespib IV 180 mg/m2
Reporting group description: -	
Reporting group title	Part A- Arm 3-Crizotinib 250 mg PO and onalespib IV 220 mg/m2
Reporting group description: -	
Reporting group title	Part B- Arm 1- Crizotinib monotherapy (250 mg PO BID)
Reporting group description: -	
Reporting group title	Part B- Arm 2- Crizotinib (250 mg) + onalespib (220 mg/m2 IV
Reporting group description: -	
Reporting group title	Part C- Arm 1- Onalespib monotherapy (260 mg/m2 IV once weekly
Reporting group description: -	
Reporting group title	Part C- Arm 2- Combin of crizotinib + onalespib

Reporting group description:

Combination of crizotinib (250 mg PO) + onalespib (220 mg/m2)

Serious adverse events	Part A- Arm 1- Crizotinib 250 mg PO and onalespib IV 150 mg/m2	Part A- Arm 2- Crizotinib 250 mg PO and onalespib IV 180 mg/m2	Part A- Arm 3- Crizotinib 250 mg PO and onalespib IV 220 mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	4 / 9 (44.44%)	6 / 15 (40.00%)
number of deaths (all causes)	7	5	8
number of deaths resulting from adverse events	0	0	1
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Syncope			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Phlebitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 stent restenosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Diplegia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Accidental overdose			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Scrotal abscess			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Breast cancer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
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 failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Tracheal stenosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Atelectasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Seizure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Hypophagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Hepatocellular injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (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
Chemical peritonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Congenital, familial and genetic disorders			
Orchitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Pericardial effusion			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
ECG QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Aphasia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 meninges			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Perineal abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Jugular vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Deep vein thrombosis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Vision blurred			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Colitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Thoracic vertebral fracture			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (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
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Gait disturbance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 infective			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Infectious pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Nosocomial infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 aspiration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Post procedural infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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 of male external genital organ			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Cholestasis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Salmonella bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (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

Serious adverse events	Part B- Arm 1- Crizotinib monotherapy (250 mg PO BID)	Part B- Arm 2- Crizotinib (250 mg) + onalespib (220 mg/m2 IV	Part C- Arm 1- Onalespib monotherapy (260 mg/m2 IV once weekly
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 66 (18.18%)	22 / 67 (32.84%)	11 / 24 (45.83%)
number of deaths (all causes)	10	11	17
number of deaths resulting from adverse events	0	1	0
Vascular disorders			
Embolism			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Phlebitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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 haematoma			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 24 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Vascular stent restenosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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			
General physical health deterioration			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Hemiparesis			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 66 (4.55%)	0 / 67 (0.00%)	0 / 24 (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
Fatigue			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (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
Asthenia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Diplegia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Fall			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Accidental overdose			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal abscess			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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			
Hypersensitivity			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast cancer			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	2 / 24 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 24 (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
Interstitial lung disease			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Pleural effusion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Tracheal stenosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Atelectasis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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			
Seizure			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 24 (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
Hypophagia			

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Mental status changes			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Cellulitis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hepatocellular injury			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Chemical peritonitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Congenital, familial and genetic disorders			
Orchitis			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
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			
Pericardial effusion			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
ECG QT prolonged			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Metastases to meninges			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Perineal abscess			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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			
Jugular vein thrombosis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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

Anaemia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Deep vein thrombosis			
subjects affected / exposed	2 / 66 (3.03%)	2 / 67 (2.99%)	0 / 24 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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			
Vision blurred			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Palpitations			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
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			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colitis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Sepsis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Abdominal pain upper			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Confusional state			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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	0 / 66 (0.00%)	1 / 67 (1.49%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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			
Thoracic vertebral fracture			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	0 / 24 (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
Device related infection			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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 cord infection			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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 tract infection			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 24 (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

Cholecystitis infective			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Infectious pleural effusion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (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
Nosocomial infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Post procedural infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cellulitis of male external genital organ			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Cholestasis			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Salmonella bacteraemia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (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
Decreased appetite			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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
Hyperkalaemia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (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

Serious adverse events	Part C- Arm 2- Combin of crizotinib + onalespib		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 28 (57.14%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	1		
Vascular disorders			
Embolism			

subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Phlebitis				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superior vena cava syndrome				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular stent restenosis				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				

subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diplegia				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant pleural effusion				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scrotal abscess			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Breast cancer			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			

subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tracheal stenosis				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Seizure				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypophagia				

subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Hepatocellular injury				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chemical peritonitis				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Orchitis				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ECG QT prolonged			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perineal abscess			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Anaemia				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Vision blurred				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Vomiting				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Colitis				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic pain				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Inappropriate antidiuretic hormone secretion				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Thoracic vertebral fracture			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cholecystitis infective			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious pleural effusion			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nosocomial infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholestasis			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salmonella bacteraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A- Arm 1- Crizotinib 250 mg PO and onalespib IV 150 mg/m2	Part A- Arm 2- Crizotinib 250 mg PO and onalespib IV 180 mg/m2	Part A- Arm 3- Crizotinib 250 mg PO and onalespib IV 220 mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	9 / 9 (100.00%)	11 / 15 (73.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Flushing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	1 / 15 (6.67%)
occurrences (all)	0	3	1
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	5	0
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	0	2	2
Vascular pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 8 (100.00%)	9 / 9 (100.00%)	10 / 15 (66.67%)
occurrences (all)	20	20	14
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	0	4	5
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
Anal fissure			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 8 (0.00%)	4 / 9 (44.44%)	0 / 15 (0.00%)
occurrences (all)	0	10	0
Early satiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Face oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Gait disturbance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Generalised oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Infusion site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infusion site pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			

subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences (all)	0	4	3
Localised oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	3 / 8 (37.50%)	3 / 9 (33.33%)	5 / 15 (33.33%)
occurrences (all)	6	5	6
Pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	1	2	2
Temperature intolerance			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	4 / 8 (50.00%)	4 / 9 (44.44%)	6 / 15 (40.00%)
occurrences (all)	6	4	10
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pneumonitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 8 (37.50%)	2 / 9 (22.22%)	6 / 15 (40.00%)
occurrences (all)	5	2	7
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Laryngeal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lung disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	4

Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	1	5
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Anxiety			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Depression			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Hallucination			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 9 (33.33%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	0	10	10
Lymphocyte count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	11	12
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	0	4	13
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	4
Weight decreased			
subjects affected / exposed	3 / 8 (37.50%)	2 / 9 (22.22%)	6 / 15 (40.00%)
occurrences (all)	3	3	8
Aspartate transaminase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	0	7	10
Blood creatine phosphokinase increased			

subjects affected / exposed	3 / 8 (37.50%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	1	5
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	4
Blood phosphorus decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Breath sounds abnormal			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	2	3	0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	2	1	3
International normalised ratio increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Protein urine present			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	10	6

Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Burn oesophageal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Eye contusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	0	6	4
Infusion related reaction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	0	1	6
Procedural pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Ventricular extrasystoles			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences (all)	0	4	1
Aphasia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Balance disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cauda equina syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cognitive disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 8 (25.00%)	4 / 9 (44.44%)	8 / 15 (53.33%)
occurrences (all)	2	4	11
Dysgeusia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	4 / 15 (26.67%)
occurrences (all)	2	2	5
Headache			
subjects affected / exposed	3 / 8 (37.50%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	3	2	3
Hypoaesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2

Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	1	3	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Restless legs syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	4 / 9 (44.44%)	6 / 15 (40.00%)
occurrences (all)	0	13	16
Iron deficiency anaemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Lymph node pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Neutropenia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Ear congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Hypoacusis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eye swelling			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Eyelid oedema			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Periorbital oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Photophobia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Photopsia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Vision blurred			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Visual impairment			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Vitreous floaters			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 8 (87.50%)	8 / 9 (88.89%)	11 / 15 (73.33%)
occurrences (all)	21	31	43
Vomiting			
subjects affected / exposed	5 / 8 (62.50%)	5 / 9 (55.56%)	7 / 15 (46.67%)
occurrences (all)	7	21	12
Nausea			
subjects affected / exposed	7 / 8 (87.50%)	6 / 9 (66.67%)	9 / 15 (60.00%)
occurrences (all)	11	17	15
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	0	4	2
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	3 / 9 (33.33%)	0 / 15 (0.00%)
occurrences (all)	1	3	0
Acquired oesophageal web			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	2 / 8 (25.00%)	3 / 9 (33.33%)	4 / 15 (26.67%)
occurrences (all)	2	5	6
Dry mouth			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	5 / 15 (33.33%)
occurrences (all)	3	2	5
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	1	1	3
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Epigastric discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Eructation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Faeces discoloured			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	9
Oesophageal ulcer			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Cholestasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Hepatic pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	4
Dry skin			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Night sweats			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	5
Rash			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	4	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nocturia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	0	5	4
Back pain			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	4 / 15 (26.67%)
occurrences (all)	1	0	5
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	0	1	3
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences (all)	2	3	1
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	9	1	0
Tendonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Herpes zoster			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Lung infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Oesophageal candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences (all)	0	2	1

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 8 (62.50%)	5 / 9 (55.56%)	8 / 15 (53.33%)
occurrences (all)	6	9	16
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	0	1	3
Hyperglycemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	3	1
Hyperkalemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Hypocalcemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	4 / 15 (26.67%)
occurrences (all)	1	1	8
Hyponatremia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	5	0
Malnutrition			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	3 / 15 (20.00%)
occurrences (all)	0	11	15
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	5 / 15 (33.33%)
occurrences (all)	1	1	6
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1

Non-serious adverse events	Part B- Arm 1- Crizotinib monotherapy (250	Part B- Arm 2- Crizotinib (250 mg) + onalespib (220	Part C- Arm 1- Onalespib monotherapy (260

	mg PO BID)	mg/m2 IV	mg/m2 IV once weekly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 66 (98.48%)	66 / 67 (98.51%)	24 / 24 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Seborrhoeic keratosis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	2 / 24 (8.33%)
occurrences (all)	1	2	7
Hot flush			
subjects affected / exposed	2 / 66 (3.03%)	4 / 67 (5.97%)	0 / 24 (0.00%)
occurrences (all)	2	6	0
Hypertension			
subjects affected / exposed	3 / 66 (4.55%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	3	4	1
Hypotension			
subjects affected / exposed	1 / 66 (1.52%)	5 / 67 (7.46%)	0 / 24 (0.00%)
occurrences (all)	1	6	0
Vascular pain			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 66 (24.24%)	32 / 67 (47.76%)	11 / 24 (45.83%)
occurrences (all)	23	90	17
Asthenia			
subjects affected / exposed	6 / 66 (9.09%)	11 / 67 (16.42%)	6 / 24 (25.00%)
occurrences (all)	7	29	7

General physical health deterioration			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Anal fissure			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	3 / 66 (4.55%)	4 / 67 (5.97%)	1 / 24 (4.17%)
occurrences (all)	3	5	1
Chest pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	7 / 66 (10.61%)	8 / 67 (11.94%)	1 / 24 (4.17%)
occurrences (all)	9	17	1
Early satiety			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	2 / 66 (3.03%)	9 / 67 (13.43%)	0 / 24 (0.00%)
occurrences (all)	3	10	0
Gait disturbance			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	1	3	1
Generalised oedema			
subjects affected / exposed	4 / 66 (6.06%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	5	1	0
Influenza like illness			
subjects affected / exposed	2 / 66 (3.03%)	1 / 67 (1.49%)	3 / 24 (12.50%)
occurrences (all)	2	1	3
Infusion site bruising			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infusion site pain			
subjects affected / exposed	0 / 66 (0.00%)	6 / 67 (8.96%)	3 / 24 (12.50%)
occurrences (all)	0	9	3

Injection site pain			
subjects affected / exposed	0 / 66 (0.00%)	4 / 67 (5.97%)	0 / 24 (0.00%)
occurrences (all)	0	27	0
Injection site reaction			
subjects affected / exposed	0 / 66 (0.00%)	4 / 67 (5.97%)	0 / 24 (0.00%)
occurrences (all)	0	4	0
Localised oedema			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	2 / 24 (8.33%)
occurrences (all)	1	1	2
Non-cardiac chest pain			
subjects affected / exposed	5 / 66 (7.58%)	3 / 67 (4.48%)	3 / 24 (12.50%)
occurrences (all)	7	3	3
Oedema peripheral			
subjects affected / exposed	16 / 66 (24.24%)	23 / 67 (34.33%)	3 / 24 (12.50%)
occurrences (all)	20	55	5
Pain			
subjects affected / exposed	3 / 66 (4.55%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	3	6	1
Peripheral swelling			
subjects affected / exposed	4 / 66 (6.06%)	4 / 67 (5.97%)	0 / 24 (0.00%)
occurrences (all)	7	6	0
Pyrexia			
subjects affected / exposed	8 / 66 (12.12%)	10 / 67 (14.93%)	2 / 24 (8.33%)
occurrences (all)	11	13	2
Temperature intolerance			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 66 (12.12%)	11 / 67 (16.42%)	1 / 24 (4.17%)
occurrences (all)	16	17	1
Pulmonary embolism			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Pneumonitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	13 / 66 (19.70%)	18 / 67 (26.87%)	3 / 24 (12.50%)
occurrences (all)	17	26	4
Dysphonia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Dyspnoea exertional			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 66 (0.00%)	3 / 67 (4.48%)	2 / 24 (8.33%)
occurrences (all)	0	3	2
Hiccups			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	2 / 24 (8.33%)
occurrences (all)	1	7	2
Laryngeal inflammation			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lung disorder			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	5 / 66 (7.58%)	9 / 67 (13.43%)	0 / 24 (0.00%)
occurrences (all)	6	18	0
Productive cough			
subjects affected / exposed	10 / 66 (15.15%)	11 / 67 (16.42%)	1 / 24 (4.17%)
occurrences (all)	17	15	1
Rales			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	3 / 66 (4.55%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 66 (1.52%)	7 / 67 (10.45%)	0 / 24 (0.00%)
occurrences (all)	1	8	0
Sinus congestion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Confusional state			
subjects affected / exposed	3 / 66 (4.55%)	1 / 67 (1.49%)	2 / 24 (8.33%)
occurrences (all)	5	2	2
Depression			
subjects affected / exposed	3 / 66 (4.55%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	4	1	0
Hallucination			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	8 / 66 (12.12%)	21 / 67 (31.34%)	6 / 24 (25.00%)
occurrences (all)	11	32	6
Investigations			
Neutrophil count decreased			
subjects affected / exposed	5 / 66 (7.58%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	4	0	3
Lymphocyte count decreased			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	6	4	0
Alanine aminotransferase increased			
subjects affected / exposed	12 / 66 (18.18%)	13 / 67 (19.40%)	2 / 24 (8.33%)
occurrences (all)	23	25	2
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Weight decreased			
subjects affected / exposed	5 / 66 (7.58%)	8 / 67 (11.94%)	2 / 24 (8.33%)
occurrences (all)	5	17	2
Aspartate transaminase increased			

subjects affected / exposed	10 / 66 (15.15%)	9 / 67 (13.43%)	1 / 24 (4.17%)
occurrences (all)	19	17	1
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 66 (13.64%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	20	6	0
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 66 (6.06%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	6	3	0
Blood bilirubin increased			
subjects affected / exposed	2 / 66 (3.03%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	4	0	0
Blood creatinine increased			
subjects affected / exposed	4 / 66 (6.06%)	5 / 67 (7.46%)	0 / 24 (0.00%)
occurrences (all)	4	13	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Breath sounds abnormal			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 66 (7.58%)	11 / 67 (16.42%)	1 / 24 (4.17%)
occurrences (all)	6	16	2
International normalised ratio increased			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Protein urine present			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 66 (0.00%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	0	4	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Burn oesophageal			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Eye contusion			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 66 (0.00%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Infusion related reaction			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Procedural pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Sinus bradycardia			

subjects affected / exposed	2 / 66 (3.03%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Tachycardia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	1	3	1
Aphasia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Balance disorder			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Cauda equina syndrome			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
Dizziness			
subjects affected / exposed	14 / 66 (21.21%)	17 / 67 (25.37%)	4 / 24 (16.67%)
occurrences (all)	17	30	4
Dysgeusia			
subjects affected / exposed	10 / 66 (15.15%)	20 / 67 (29.85%)	2 / 24 (8.33%)
occurrences (all)	10	30	2
Headache			
subjects affected / exposed	17 / 66 (25.76%)	18 / 67 (26.87%)	9 / 24 (37.50%)
occurrences (all)	21	28	11
Hypoaesthesia			
subjects affected / exposed	0 / 66 (0.00%)	6 / 67 (8.96%)	0 / 24 (0.00%)
occurrences (all)	0	9	0

Neuralgia			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Neuropathy peripheral			
subjects affected / exposed	3 / 66 (4.55%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	3	2	0
Paraesthesia			
subjects affected / exposed	0 / 66 (0.00%)	8 / 67 (11.94%)	1 / 24 (4.17%)
occurrences (all)	0	11	1
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 66 (7.58%)	6 / 67 (8.96%)	1 / 24 (4.17%)
occurrences (all)	6	7	1
Presyncope			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Restless legs syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	2 / 66 (3.03%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	2	2	0
Tremor			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 66 (10.61%)	10 / 67 (14.93%)	2 / 24 (8.33%)
occurrences (all)	8	14	2
Iron deficiency anaemia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lymph node pain			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Lymphopenia			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Neutropenia			
subjects affected / exposed	2 / 66 (3.03%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	4	12	0
Thrombocytopenia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Ear congestion			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	4 / 66 (6.06%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	4	5	1
Vertigo			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	2 / 66 (3.03%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	2	1	0
Eye pain			

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Periorbital oedema			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Photopsia			
subjects affected / exposed	12 / 66 (18.18%)	12 / 67 (17.91%)	3 / 24 (12.50%)
occurrences (all)	15	18	3
Vision blurred			
subjects affected / exposed	3 / 66 (4.55%)	2 / 67 (2.99%)	3 / 24 (12.50%)
occurrences (all)	4	3	4
Visual impairment			
subjects affected / exposed	11 / 66 (16.67%)	12 / 67 (17.91%)	2 / 24 (8.33%)
occurrences (all)	15	18	2
Vitreous floaters			
subjects affected / exposed	3 / 66 (4.55%)	4 / 67 (5.97%)	1 / 24 (4.17%)
occurrences (all)	3	5	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	34 / 66 (51.52%)	55 / 67 (82.09%)	18 / 24 (75.00%)
occurrences (all)	75	393	44
Vomiting			
subjects affected / exposed	26 / 66 (39.39%)	44 / 67 (65.67%)	9 / 24 (37.50%)
occurrences (all)	53	191	13

Nausea			
subjects affected / exposed	35 / 66 (53.03%)	51 / 67 (76.12%)	11 / 24 (45.83%)
occurrences (all)	56	145	35
Abdominal discomfort			
subjects affected / exposed	1 / 66 (1.52%)	4 / 67 (5.97%)	1 / 24 (4.17%)
occurrences (all)	1	4	1
Abdominal distension			
subjects affected / exposed	1 / 66 (1.52%)	4 / 67 (5.97%)	1 / 24 (4.17%)
occurrences (all)	1	4	1
Abdominal pain			
subjects affected / exposed	4 / 66 (6.06%)	14 / 67 (20.90%)	5 / 24 (20.83%)
occurrences (all)	5	18	6
Abdominal pain upper			
subjects affected / exposed	7 / 66 (10.61%)	11 / 67 (16.42%)	1 / 24 (4.17%)
occurrences (all)	14	16	1
Acquired oesophageal web			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	23 / 66 (34.85%)	27 / 67 (40.30%)	3 / 24 (12.50%)
occurrences (all)	38	44	5
Dry mouth			
subjects affected / exposed	3 / 66 (4.55%)	14 / 67 (20.90%)	7 / 24 (29.17%)
occurrences (all)	4	23	9
Dyspepsia			
subjects affected / exposed	7 / 66 (10.61%)	15 / 67 (22.39%)	2 / 24 (8.33%)
occurrences (all)	13	29	2
Dysphagia			
subjects affected / exposed	3 / 66 (4.55%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	3	2	0
Epigastric discomfort			
subjects affected / exposed	2 / 66 (3.03%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	3	3	0
Eructation			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Faeces discoloured			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 66 (3.03%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	2	2	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Oesophageal ulcer			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	2 / 66 (3.03%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	2	1	0
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Cholestasis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hepatic pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Dry skin			

subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	1 / 24 (4.17%)
occurrences (all)	1	5	1
Hyperhidrosis			
subjects affected / exposed	1 / 66 (1.52%)	6 / 67 (8.96%)	1 / 24 (4.17%)
occurrences (all)	1	12	1
Night sweats			
subjects affected / exposed	0 / 66 (0.00%)	4 / 67 (5.97%)	1 / 24 (4.17%)
occurrences (all)	0	7	1
Pruritus			
subjects affected / exposed	6 / 66 (9.09%)	7 / 67 (10.45%)	2 / 24 (8.33%)
occurrences (all)	6	17	2
Rash			
subjects affected / exposed	9 / 66 (13.64%)	13 / 67 (19.40%)	3 / 24 (12.50%)
occurrences (all)	12	29	3
Rash maculo-papular			
subjects affected / exposed	2 / 66 (3.03%)	4 / 67 (5.97%)	2 / 24 (8.33%)
occurrences (all)	2	6	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 66 (4.55%)	5 / 67 (7.46%)	0 / 24 (0.00%)
occurrences (all)	4	8	0
Nocturia			
subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Pollakiuria			
subjects affected / exposed	0 / 66 (0.00%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Urinary retention			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	4 / 66 (6.06%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	4	7	0
Back pain			
subjects affected / exposed	4 / 66 (6.06%)	7 / 67 (10.45%)	3 / 24 (12.50%)
occurrences (all)	5	10	4
Arthralgia			
subjects affected / exposed	3 / 66 (4.55%)	4 / 67 (5.97%)	2 / 24 (8.33%)
occurrences (all)	3	4	2
Bone pain			
subjects affected / exposed	0 / 66 (0.00%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Flank pain			
subjects affected / exposed	4 / 66 (6.06%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	5	0	0
Groin pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	2 / 66 (3.03%)	7 / 67 (10.45%)	3 / 24 (12.50%)
occurrences (all)	4	10	4
Musculoskeletal chest pain			
subjects affected / exposed	3 / 66 (4.55%)	4 / 67 (5.97%)	3 / 24 (12.50%)
occurrences (all)	3	4	4
Musculoskeletal pain			
subjects affected / exposed	6 / 66 (9.09%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	6	4	0
Myalgia			
subjects affected / exposed	3 / 66 (4.55%)	12 / 67 (17.91%)	1 / 24 (4.17%)
occurrences (all)	4	24	1
Neck pain			

subjects affected / exposed	3 / 66 (4.55%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Pain in extremity			
subjects affected / exposed	4 / 66 (6.06%)	5 / 67 (7.46%)	3 / 24 (12.50%)
occurrences (all)	4	9	3
Tendonitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Cellulitis			
subjects affected / exposed	0 / 66 (0.00%)	3 / 67 (4.48%)	0 / 24 (0.00%)
occurrences (all)	0	6	0
Herpes zoster			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	5 / 66 (7.58%)	7 / 67 (10.45%)	1 / 24 (4.17%)
occurrences (all)	5	7	1
Oesophageal candidiasis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	1	2	0

Sinusitis			
subjects affected / exposed	0 / 66 (0.00%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 66 (3.03%)	4 / 67 (5.97%)	0 / 24 (0.00%)
occurrences (all)	3	4	0
Urinary tract infection			
subjects affected / exposed	5 / 66 (7.58%)	8 / 67 (11.94%)	1 / 24 (4.17%)
occurrences (all)	6	13	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 66 (24.24%)	24 / 67 (35.82%)	10 / 24 (41.67%)
occurrences (all)	17	56	10
Dehydration			
subjects affected / exposed	2 / 66 (3.03%)	4 / 67 (5.97%)	0 / 24 (0.00%)
occurrences (all)	2	6	0
Hyperglycemia			
subjects affected / exposed	3 / 66 (4.55%)	1 / 67 (1.49%)	1 / 24 (4.17%)
occurrences (all)	5	1	1
Hyperkalemia			
subjects affected / exposed	3 / 66 (4.55%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	3	4	0
Hypocalcemia			
subjects affected / exposed	5 / 66 (7.58%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	10	3	0
Hyponatremia			
subjects affected / exposed	3 / 66 (4.55%)	1 / 67 (1.49%)	1 / 24 (4.17%)
occurrences (all)	4	1	4
Malnutrition			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	6 / 66 (9.09%)	4 / 67 (5.97%)	0 / 24 (0.00%)
occurrences (all)	8	7	0
Hypoglycaemia			

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	7 / 66 (10.61%)	5 / 67 (7.46%)	1 / 24 (4.17%)
occurrences (all)	11	11	1
Hypophosphataemia			
subjects affected / exposed	1 / 66 (1.52%)	2 / 67 (2.99%)	0 / 24 (0.00%)
occurrences (all)	1	2	0

Non-serious adverse events	Part C- Arm 2- Combin of crizotinib + onalespib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Seborrhoeic keratosis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Hot flush			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Vascular pain			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 28 (42.86%)		
occurrences (all)	24		
Asthenia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
General physical health deterioration			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Chest discomfort			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Early satiety			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Face oedema			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Gait disturbance			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	4		
Generalised oedema			

subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Influenza like illness				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Infusion site bruising				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Infusion site pain				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Injection site pain				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Injection site reaction				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Localised oedema				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Malaise				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Non-cardiac chest pain				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	2			
Oedema peripheral				
subjects affected / exposed	8 / 28 (28.57%)			
occurrences (all)	15			
Pain				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	2			
Peripheral swelling				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Pyrexia				

subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Temperature intolerance			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Thirst			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	7		
Pulmonary embolism			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Pneumonitis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	8		
Dysphonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Haemoptysis			

subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	5			
Hiccups				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Laryngeal inflammation				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Lung disorder				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Nasal congestion				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Oropharyngeal pain				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Productive cough				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Rales				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Respiratory tract congestion				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Rhinitis allergic				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Rhinorrhoea				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Sinus congestion				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Upper-airway cough syndrome				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Hallucination			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	37		
Lymphocyte count decreased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Alanine aminotransferase increased			

subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	3			
Activated partial thromboplastin time prolonged				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Weight decreased				
subjects affected / exposed	6 / 28 (21.43%)			
occurrences (all)	7			
Aspartate transaminase increased				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Blood alkaline phosphatase increased				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Blood bilirubin increased				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Blood phosphorus decreased				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Breath sounds abnormal				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
International normalised ratio increased				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Protein urine present			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Burn oesophageal			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Eye contusion			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Infusion related reaction			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Procedural pain			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Traumatic haematoma			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Ventricular extrasystoles			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Aphasia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Balance disorder			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cauda equina syndrome			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Cognitive disorder			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Dizziness			

subjects affected / exposed	5 / 28 (17.86%)			
occurrences (all)	5			
Dysgeusia				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	5 / 28 (17.86%)			
occurrences (all)	7			
Hypoaesthesia				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	4			
Neuralgia				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Neuropathy peripheral				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Paraesthesia				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Peripheral sensory neuropathy				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Presyncope				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Restless legs syndrome				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	2			
Somnolence				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Tremor				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	3			
Vasogenic cerebral oedema				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	8		
Iron deficiency anaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Lymph node pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	5		
Thrombocytopenia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Ear congestion			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hypoacusis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Vertigo			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Diplopia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Eye swelling			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Periorbital oedema			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Photopsia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		
Visual impairment			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		

Vitreous floaters			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 28 (71.43%)		
occurrences (all)	41		
Vomiting			
subjects affected / exposed	15 / 28 (53.57%)		
occurrences (all)	32		
Nausea			
subjects affected / exposed	20 / 28 (71.43%)		
occurrences (all)	28		
Abdominal discomfort			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Acquired oesophageal web			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences (all)	10		
Dry mouth			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Dyspepsia			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	4		
Dysphagia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Epigastric discomfort			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Eructation			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Faeces discoloured			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Oesophageal ulcer			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

Cholestasis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hepatic pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Night sweats			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	5		
Rash maculo-papular			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Nocturia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Pollakiuria			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Urinary retention			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hypothyroidism			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Arthralgia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Groin pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Musculoskeletal chest pain			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	6		
Neck pain			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Lung infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		

Oesophageal candidiasis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0			
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3			
Rhinitis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0			
Sinusitis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1			
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1			
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 28 (21.43%) 10			
Dehydration subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3			
Hyperglycemia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1			
Hyperkalemia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2			
Hypocalcemia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 4			
Hyponatremia				

subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	7		
Malnutrition			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypoglycaemia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2012	-Added Inclusion Criterion #3, so that subjects enrolled in Part A could have evaluable disease, rather than just measurable disease per RECIST. -Clarified Inclusion Criteria #2 and #4, such that subjects who had other prior anticancer therapies, including other ALK inhibitors, could be enrolled in the study, while still requiring at least 8 weeks of prior crizotinib exposure. -Added a requirement that, if neither archival nor pre-existing tumor tissue were available, a sample must be obtained, if safe and appropriate, during screening in Part A.
17 April 2014	-Modified Inclusion Criterion #3, to remove requirement for measurable disease to allow subjects who no longer had measurable disease during crizotinib treatment to be enrolled in Part B. -Modified Inclusion Criterion #4b (enrollment in Part B), to remove requirement for at least 8 weeks of prior treatment with crizotinib. -Modified Inclusion Criterion #4b to permit enrollment of subjects who were currently receiving and tolerating crizotinib and had not progressed by RECIST 1.1 or who had not yet started but were eligible to receive crizotinib. -Changed the primary endpoint in Part B to PFS (rather than objective response), since assessment of objective response would not be possible in subjects who did not have measurable disease at baseline. -Clarified Inclusion Criterion #4c (enrollment in Part C), to permit enrollment of subjects who had previously received other therapy including other ALK inhibitors before enrollment). -Modified Inclusion Criterion #9 to change the maximum allowed QTc interval from 450 to 480 msec. -Modified Exclusion Criterion #5 to clarify that exclusionary QTc prolongation (>480 msec) must be related to crizotinib on multiple measurements. -Modified Exclusion Criterion #6 to clarify that Grade 2 bilirubin or transaminases on multiple measurements must be related to crizotinib while receiving crizotinib. -Modified Exclusion Criterion #7 to clarify that Grade 2 visual disturbances must be related to crizotinib while receiving crizotinib. -Updated study objectives, endpoints, analyses, and discussion of study design to reflect changes due to the elimination of the requirement for measurable disease in Part B. -Updated power calculation for Part B. Sample size will provide 82% power to detect a difference between a median PFS of 5 months (control group of crizotinib alone) and 9 months (experimental group of crizotinib + onalespib) with 2-sided log-rank test at an α level of 0.05.
28 March 2016	- The study design was modified to add Part D so that subjects in South Korea could continue to receive crizotinib alone, if deemed appropriated by their physician. - In Part D, study assessments were reduced to collection (and reporting) of reported SAEs only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

For this summary, we have used Part A as an overall baseline.

Notes: