

**Clinical trial results:****A Phase 1/2 Study of PF-02341066, an Oral Small Molecule Inhibitor of Anaplastic Lymphoma Kinase (ALK) and C-Met, in Children With Relapsed/Refractory Solid Tumors and Anaplastic Large Cell Lymphoma
Summary**

EudraCT number	2020-003468-19
Trial protocol	Outside EU/EEA
Global end of trial date	19 January 2018

Results information

Result version number	v1 (current)
This version publication date	11 November 2020
First version publication date	11 November 2020

Trial information**Trial identification**

Sponsor protocol code	ADVL0912
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00939770
WHO universal trial number (UTN)	-
Other trial identifiers	Clinical Trial Reporting Program: NCI-2011-01937

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001493-PIP03-18
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 May 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To estimate the maximum tolerated dose (MTD) and recommend a Phase 2 dose of Crizotinib administered orally twice daily to children with relapsed/refractory solid tumors and anaplastic large cell lymphoma (ALCL). •To define and describe the toxicities of Crizotinib administered on this schedule. •To characterise the pharmacokinetics of Crizotinib in children with refractory cancer.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2009
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	United States: 118
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	122
EEA total number of subjects	0

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)	1
Children (2-11 years)	77
Adolescents (12-17 years)	28
Adults (18-64 years)	16
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Study was conducted in the United States and Canada from 29 September 2009 to 19 January 2018. A total of 122 subjects were enrolled, out of which only 121 received treatment.

Pre-assignment

Screening details:

Study was conducted in 2 phases. Phase 1 was the dose finding part and Phase 2 was the dose expansion conducted on the maximum tolerated dose (MTD) identified in Phase 1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group

Arm description:

Subjects with anaplastic lymphoma kinase (ALK)-positive ALCL, received Crizotinib, orally, twice daily (BID) in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Subjects received 165 milligram per meter square (mg/m^2) (Phase 1) and 280 mg/m^2 (Phase 1 and 2) doses of crizotinib.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	Xalkori
Pharmaceutical forms	Oral solution, Powder for oral solution, Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects with ALK-positive ALCL, received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy. Subjects received 165 mg/m^2 (Phase 1) and 280 mg/m^2 (Phase 1 and 2) doses of crizotinib.

Arm title	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group
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Arm description:

Subjects with ALK-positive IMT, received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Starting dose of crizotinib was 100 mg/m^2 in Phase 1 which was escalated as 165 mg/m^2 (Phase 1) and 280 mg/m^2 (Phase 2).

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	Xalkori
Pharmaceutical forms	Oral solution, Powder for oral solution, Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects with ALK-positive IMT, received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy. Starting dose of crizotinib was 100 mg/m^2 in Phase 1 which was escalated as 165 mg/m^2 (Phase 1) and 280 mg/m^2 (Phase 2).

Arm title	Phase 1 and 2: Other Tumors Group
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Arm description:

Subjects with ALK-positive neuroblastoma (NB), received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Starting dose of crizotinib was 100 mg/m² in Phase 1 which was escalated as 130, 165, 215, 280 and up to 365 mg/m² (Phase 1 and 2).

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	Xalkori
Pharmaceutical forms	Oral solution, Powder for oral solution, Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects with ALK-positive neuroblastoma (NB), received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy. Starting dose of crizotinib was 100 mg/m² in Phase 1 which was escalated as 130, 165, 215, 280 and up to 365 mg/m² (Phase 1 and 2).

Number of subjects in period 1	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group	Phase 1 and 2: Other Tumors Group
Started	26	14	82
Treated	26	14	81
Completed	2	3	1
Not completed	24	11	81
Therapy refusal by Patient/Parent/Guardian	7	1	8
Consent withdrawn by subject	1	-	-
Physician decision	8	4	1
Adverse Event	2	4	6
Progressive Disease	3	-	65
Enrolled but not Treated	-	-	1
Non-Compliance With Study Drug	1	2	-
Lost to follow-up	1	-	-
No Longer Meets Eligibility Criteria	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group
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Reporting group description:

Subjects with anaplastic lymphoma kinase (ALK)-positive ALCL, received Crizotinib, orally, twice daily (BID) in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Subjects received 165 milligram per meter square (mg/m²) (Phase 1) and 280 mg/m² (Phase 1 and 2) doses of crizotinib.

Reporting group title	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group
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Reporting group description:

Subjects with ALK-positive IMT, received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Starting dose of crizotinib was 100 mg/m² in Phase 1 which was escalated as 165 mg/m² (Phase 1) and 280 mg/m² (Phase 2).

Reporting group title	Phase 1 and 2: Other Tumors Group
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Reporting group description:

Subjects with ALK-positive neuroblastoma (NB), received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Starting dose of crizotinib was 100 mg/m² in Phase 1 which was escalated as 130, 165, 215, 280 and up to 365 mg/m² (Phase 1 and 2).

Reporting group values	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group	Phase 1 and 2: Other Tumors Group
Number of subjects	26	14	82
Age Categorical Units: Subjects			
<2 years	0	0	1
2-<6 years	4	4	18
6-<12 years	11	8	32
12-<18 years	7	2	19
18-21 years	4	0	12
Age Continuous			
Data reported for 121 subjects.			
Units: years			
arithmetic mean	11.2	7.1	10.0
standard deviation	± 5.02	± 3.53	± 5.35
Gender Categorical Units: Subjects			
Female	8	9	43
Male	18	5	39
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	3	7
Not Hispanic or Latino	22	8	68
Unknown or Not Reported	1	3	7
Race (NIH/OMB) Units: Subjects			
Asian	2	0	4
Black or African American	5	1	5

White	14	10	63
Unknown or Not Reported	5	3	10

Reporting group values	Total		
Number of subjects	122		
Age Categorical Units: Subjects			
<2 years	1		
2-<6 years	26		
6-<12 years	51		
12-<18 years	28		
18-21 years	16		
Age Continuous			
Data reported for 121 subjects.			
Units: years arithmetic mean standard deviation	-		
Gender Categorical Units: Subjects			
Female	60		
Male	62		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13		
Not Hispanic or Latino	98		
Unknown or Not Reported	11		
Race (NIH/OMB) Units: Subjects			
Asian	6		
Black or African American	11		
White	87		
Unknown or Not Reported	18		

End points

End points reporting groups

Reporting group title	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group
Reporting group description: Subjects with anaplastic lymphoma kinase (ALK)-positive ALCL, received Crizotinib, orally, twice daily (BID) in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Subjects received 165 milligram per meter square (mg/m ²) (Phase 1) and 280 mg/m ² (Phase 1 and 2) doses of crizotinib.	
Reporting group title	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group
Reporting group description: Subjects with ALK-positive IMT, received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Starting dose of crizotinib was 100 mg/m ² in Phase 1 which was escalated as 165 mg/m ² (Phase 1) and 280 mg/m ² (Phase 2).	
Reporting group title	Phase 1 and 2: Other Tumors Group
Reporting group description: Subjects with ALK-positive neuroblastoma (NB), received Crizotinib, orally, BID in each cycle of 28 days until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months). Starting dose of crizotinib was 100 mg/m ² in Phase 1 which was escalated as 130, 165, 215, 280 and up to 365 mg/m ² (Phase 1 and 2).	
Subject analysis set title	Phase 1: Crizotinib 100 mg/m ² BID
Subject analysis set type	Per protocol
Subject analysis set description: In Phase 1, subjects received Crizotinib at a dose of 100 mg/m ² , orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).	
Subject analysis set title	Phase 1: Crizotinib 130 mg/m ² BID
Subject analysis set type	Per protocol
Subject analysis set description: In Phase 1, subjects received Crizotinib at a dose of 130 mg/m ² , orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).	
Subject analysis set title	Phase 1: Crizotinib 165 mg/m ² BID
Subject analysis set type	Per protocol
Subject analysis set description: In Phase 1, subjects received Crizotinib at a dose of 165 mg/m ² , orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).	
Subject analysis set title	Phase 1: Crizotinib 215 mg/m ² BID
Subject analysis set type	Per protocol
Subject analysis set description: In Phase 1, subjects received Crizotinib at a dose of 215 mg/m ² , orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).	
Subject analysis set title	Phase 1: Crizotinib 280 mg/m ² BID
Subject analysis set type	Per protocol
Subject analysis set description: In Phase 1, subjects received Crizotinib at a dose of 280 mg/m ² , orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).	
Subject analysis set title	Phase 1: Crizotinib 365 mg/m ² BID
Subject analysis set type	Per protocol
Subject analysis set description: In Phase 1, subjects received Crizotinib at a dose of 365 mg/m ² , orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).	
Subject analysis set title	ALCL: Crizotinib 165 mg/m ² BID
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or ALCL received Crizotinib at a dose of 165 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	ALCL: Crizotinib 280 mg/m ² BID
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or ALCL received Crizotinib at a dose of 280 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	IMT: Crizotinib 100 mg/m ² BID
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or IMT received Crizotinib at a dose of 100 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	IMT: Crizotinib 165 mg/m ² BID
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or IMT received Crizotinib at a dose of 165 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	IMT: Crizotinib 280 mg/m ² BID
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or IMT received Crizotinib at a dose of 280 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	ALCL and IMT: Crizotinib 100 mg/m ² BID
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or ALCL and IMT received Crizotinib at a dose of 100 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	ALCL and IMT: Crizotinib 165 mg/m ² BID
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or ALCL and IMT received Crizotinib at a dose of 165 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	ALCL and IMT: Crizotinib 280 mg/m ² BID
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or ALCL and IMT received Crizotinib at a dose of 280 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	Total (ALCL): 165 mg/m ² BID and 280 mg/m ² BID
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or ALCL received Crizotinib at a dose of 165 mg/m² and 280 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	Total (IMT): 165 mg/m ² BID and 280 mg/m ² BID
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with relapsed/refractory solid tumors or IMT received Crizotinib at a dose of 165 mg/m² and 280 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Subject analysis set title	Phase 1: Crizotinib 280 mg/m ² BID for DLT
Subject analysis set type	Per protocol

Subject analysis set description:

In Phase 1, subjects received Crizotinib at a dose of 280 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Primary: Phase 1: Number of Subjects Reporting Dose Limiting Toxicities (DLTs) With Crizotinib

End point title	Phase 1: Number of Subjects Reporting Dose Limiting Toxicities (DLTs) With Crizotinib ^[1]
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End point description:

DLT: protocol-specified events possibly, probably or definitely attributable to crizotinib. Non-hematological DLT: Any Grade(G)4 non-hematological toxicity; Any G3 non-hematological toxicity:G3 nausea, vomiting <3 days,G3 ALT/AST return to levels that met initial eligibility criteria in 7 days of study drug interruption,G3 fever or infection <5 days, G3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation; G2 allergic reactions necessitated discontinuation of study drug were not considered DLT; Any G2 non-hematological toxicity persisted for >=7 days,was medically significant or intolerable;Any adverse event with interruption of study drug for >=7 days. Hematological DLT:G4 thrombocytopenia or G4 neutropenia. Grades based on NCI-CTCAE version 4. Only hematological toxicities reported in this endpoint. Per-protocol analysis set included subjects with DLT or without DLT. Number of subjects analysed=subjects evaluable for this endpoint.

End point type	Primary
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End point timeframe:

Cycle 1 (28 days)

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 descriptive statistics was planned to be summarized for this endpoint.

End point values	Phase 1: Crizotinib 100 mg/m ² BID	Phase 1: Crizotinib 130 mg/m ² BID	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	6	21	10
Units: subjects				
number (not applicable)	0	0	1	0

End point values	Phase 1: Crizotinib 365 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID for DLT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	26		
Units: subjects				
number (not applicable)	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Time to Reach Maximum Observed Plasma

Concentration (Tmax) of Crizotinib After Single Dose Administration

End point title	Phase 1: PK Parameter- Time to Reach Maximum Observed Plasma Concentration (Tmax) of Crizotinib After Single Dose Administration
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End point description:

PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here, 'Number of subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 280 mg/m² BID and 365 mg/m² BID dose and were not reported.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1: Pre-dose, 0.5, 1, 2, 4, 6, 8-10 and 22-26 hours post morning dose for subjects ≥ 10 kg;
Pre-dose, 1, 2, 4, 6, 8-10 and 22-26 hours post morning dose for subjects < 10 kg

End point values	Phase 1: Crizotinib 100 mg/m ² BID	Phase 1: Crizotinib 130 mg/m ² BID	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	14	2
Units: hours				
median (full range (min-max))	2 (1 to 4)	4 (2 to 6)	4 (2 to 8)	4 (4 to 4)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Maximum Observed Plasma Concentration (Cmax) of Crizotinib After Single Dose Administration

End point title	Phase 1: PK Parameter- Maximum Observed Plasma Concentration (Cmax) of Crizotinib After Single Dose Administration
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End point description:

PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here, 99999 in data field signifies that data cannot be estimated for parameters with less than 3 evaluable measurements. Here, 'Number of subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 280 mg/m² BID and 365 mg/m² BID dose and were not reported.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1: Pre-dose, 0.5, 1, 2, 4, 6, 8-10 and 22-26 hours post morning dose for subjects ≥ 10 kg;
Pre-dose, 1, 2, 4, 6, 8-10 and 22-26 hours post morning dose for subjects < 10 kg

End point values	Phase 1: Crizotinib 100 mg/m ² BID	Phase 1: Crizotinib 130 mg/m ² BID	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	14	2
Units: nanograms per millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	111.8 (± 55)	169.6 (± 75)	111.2 (± 63)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) of Crizotinib After Single Dose Administration

End point title	Phase 1: PK Parameter- Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) of Crizotinib After Single Dose Administration
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End point description:

PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here, 99999 in data field signifies that data cannot be estimated for parameters with less than 3 evaluable measurements. Here, 'Number of subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 280 mg/m² BID and 365 mg/m² BID dose and were not reported.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1: Pre-dose, 0.5, 1, 2, 4, 6, 8-10 and 22-26 hours post morning dose for subjects ≥10 kg; Pre-dose, 1, 2, 4, 6, 8-10 and 22-26 hours post morning dose for subjects <10 kg

End point values	Phase 1: Crizotinib 100 mg/m ² BID	Phase 1: Crizotinib 130 mg/m ² BID	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	4	14	2
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	921.7 (± 74)	1547 (± 151)	867.8 (± 100)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Steady State Time to Reach Maximum Observed Plasma Concentration (Tmax) of Crizotinib

End point title	Phase 1: PK Parameter- Steady State Time to Reach Maximum Observed Plasma Concentration (Tmax) of Crizotinib
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End point description:

PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here 'Number of

subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 100 mg/m² BID and 130 mg/m² BID dose and were not reported.

End point type	Secondary
End point timeframe:	
Between Days 15 and 28 in Cycle 1: pre-dose (12 hours after the last dose), 1 hour, 2 hour, 4 hours, and 6-8 hours post morning dose	

End point values	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID	Phase 1: Crizotinib 365 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	4	45	3
Units: hours				
median (full range (min-max))	5.98 (5.98 to 5.98)	4.08 (2.00 to 6.08)	4.00 (0 to 6.38)	4.00 (1.25 to 6.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Steady State Maximum Observed Plasma Concentration (C_{max}) of Crizotinib

End point title	Phase 1: PK Parameter- Steady State Maximum Observed Plasma Concentration (C _{max}) of Crizotinib
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End point description:

PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here, 99999 in data field signifies that data cannot be estimated for parameters with less than 3 evaluable measurements. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 100 mg/m² BID and 130 mg/m² BID dose and were not reported.

End point type	Secondary
End point timeframe:	
Between Days 15 and 28 in Cycle 1: pre-dose (12 hours after the last dose), 1 hour, 2 hour, 4 hours, and 6-8 hours post morning dose	

End point values	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID	Phase 1: Crizotinib 365 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	4	45	3
Units: ng/mL				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	627.5 (± 17)	631.6 (± 69)	713.7 (± 26)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Steady State Trough Plasma Concentration (C_{trough}) of Crizotinib

End point title	Phase 1: PK Parameter- Steady State Trough Plasma Concentration (C _{trough}) of Crizotinib
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End point description:

C_{trough} is the predose plasma concentration. PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here, 99999 in data field signifies that data cannot be estimated for parameters with less than 3 evaluable measurements. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 100 mg/m² BID and 130 mg/m² BID dose and were not reported.

End point type	Secondary
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End point timeframe:

Between Days 15 and 28 in Cycle 1: pre-dose (12 hours after the last dose), 1 hour, 2 hour, 4 hours, and 6-8 hours post morning dose

End point values	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID	Phase 1: Crizotinib 365 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	44	3
Units: ng/mL				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	306.0 (± 32)	459.3 (± 39)	546.4 (± 16)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Steady State Area Under the Curve from Time Zero to end of dosing interval (AUC_{tau}) of Crizotinib

End point title	Phase 1: PK Parameter- Steady State Area Under the Curve from Time Zero to end of dosing interval (AUC _{tau}) of Crizotinib
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End point description:

PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here, 99999 in data field signifies that data cannot be estimated for parameters with less than 3 evaluable measurements. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 100 mg/m² BID and 130 mg/m² BID dose and were not reported.

End point type	Secondary
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End point timeframe:

Between Days 15 and 28 in Cycle 1: pre-dose (12 hours after the last dose), 1 hour, 2 hour, 4 hours, and 6-8 hours post morning dose

End point values	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID	Phase 1: Crizotinib 365 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	44	3
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	5286 (± 14)	6621 (± 34)	6794 (± 10)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: PK Parameter- Steady State Apparent Clearance (CL/F) of Crizotinib

End point title	Phase 1: PK Parameter- Steady State Apparent Clearance (CL/F) of Crizotinib
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End point description:

Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. Clearance obtained after oral dose is influenced by the fraction of the dose absorbed. PK parameter analysis set included all enrolled subjects who received at least one dose of crizotinib and had sufficient information to estimate at least one of the PK parameters of interest. Here, 99999 in data field signifies that data cannot be estimated for parameters with less than 3 evaluable measurements. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint. None of the subjects were evaluated for 100 mg/m² BID and 130 mg/m² BID dose and were not reported.

End point type	Secondary
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End point timeframe:

Between Days 15 and 28 of BID dosing in Cycle 1, pre-dose (12 hours after the last dose), 1 hour, 2 hour, 4 hours, and 6-8 hours post morning dose

End point values	Phase 1: Crizotinib 165 mg/m ² BID	Phase 1: Crizotinib 215 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID	Phase 1: Crizotinib 365 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	44	3
Units: litres/hour				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	41.78 (± 66)	46.61 (± 54)	64.22 (± 40)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Objective Response (OR)

End point title	Percentage of Subjects With Objective Response (OR)
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End point description:

OR defined as subjects with complete response (CR), CR unconfirmed (CRu) or partial response (PR). Per Cheson criteria, (for ALCL), CR= disappearance of all evidence of disease from all sites for ≥4 weeks. CRu= ≥75% shrinkage in sums of the perpendicular diameters (SPD) of lesions and no residual

FDG PET activity; PR= $\geq 50\%$ decrease in the SPD of the lesions. As per RECIST v1.0, (for IMT), CR= disappearance of all target and non-target lesions; PR= $\geq 30\%$ decrease in sum of longest diameters (LD) of target lesions taking as a reference the baseline sum LD. Response evaluable (RE) analysis set included all randomised subjects who received study drug, had measurable or evaluable disease at baseline by investigator assessment, or had baseline disease assessment per central review. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

From randomisation to progression of disease, start of new anti-cancer therapy or discontinuation from study or death, whichever occurred first (up to 88.8 months)

End point values	ALCL: Crizotinib 165 mg/m ² BID	ALCL: Crizotinib 280 mg/m ² BID	IMT: Crizotinib 100 mg/m ² BID	IMT: Crizotinib 165 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	20	1	1
Units: percentage of subjects				
median (confidence interval 95%)	83.3 (43.6 to 97.0)	90.0 (69.9 to 97.2)	0 (0.0 to 79.3)	100 (20.7 to 100.0)

End point values	IMT: Crizotinib 280 mg/m ² BID			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: percentage of subjects				
median (confidence interval 95%)	91.7 (64.6 to 98.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Tumor Response (DR)

End point title	Duration of Objective Tumor Response (DR)
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End point description:

DR: time from first documentation of OR (CR/CRu or PR) to first documentation of objective tumor progression or death due to any cause based on central review. Per Cheson criteria, (for ALCL), CR= disappearance of all evidence of disease from all sites for ≥ 4 weeks. CRu= $\geq 75\%$ shrinkage in the SPD of the lesions and no residual FDG PET activity; PR= $\geq 50\%$ decrease in SPD lesions. As per RECIST v1.0, (for IMT), CR= disappearance of all target and non-target lesions; PR= $\geq 30\%$ decrease in sum of LD of target lesions taking as reference baseline sum LD. RE analysis set included all randomised subjects who received study drug, had measurable or evaluable disease at baseline by investigator assessment, or had baseline disease assessment per central review. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline until disease progression or death due to any cause (up to 88.8 months)

End point values	ALCL: Crizotinib 165 mg/m ² BID	ALCL: Crizotinib 280 mg/m ² BID	IMT: Crizotinib 165 mg/m ² BID	IMT: Crizotinib 280 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	18	1	11
Units: months				
median (full range (min-max))	6.9 (2.5 to 10.2)	3.0 (0.0 to 18.6)	48.9 (48.9 to 48.9)	12.7 (2.8 to 39.9)

End point values	Total (ALCL): 165 mg/m ² BID and 280 mg/m ² BID	Total (IMT): 165 mg/m ² BID and 280 mg/m ² BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	12		
Units: months				
median (full range (min-max))	3.9 (0.0 to 18.6)	14.8 (2.8 to 48.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Tumor Response (TTR)

End point title	Time to Objective Tumor Response (TTR)
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End point description:

TTR: time from first dose Cycle 1 Day 1 (C1D1) to first documentation of objective tumor response (CR/CRu or PR). Per Cheson criteria, (for ALCL), CR= disappearance of all evidence of disease from all sites for ≥ 4 weeks. CRu= $\geq 75\%$ shrinkage in the SPD of the lesions and no residual FDG PET activity; PR= $\geq 50\%$ decrease in SPD lesions. As per RECIST v1.0, (for IMT), CR= disappearance of all target and non-target lesions; PR= $\geq 30\%$ decrease in sum of LD of target lesions taking as reference baseline sum LD. RE analysis set included all randomised subjects who received study drug, had measurable or evaluable disease at baseline by investigator assessment, or had baseline disease assessment per central review. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

From the date of randomisation to the first documentation of objective response (CR or PR) (up to 88.8 months)

End point values	ALCL: Crizotinib 165 mg/m ² BID	ALCL: Crizotinib 280 mg/m ² BID	IMT: Crizotinib 165 mg/m ² BID	IMT: Crizotinib 280 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	18	1	11
Units: months				
median (full range (min-max))	0.9 (0.8 to 1.0)	0.9 (0.8 to 2.1)	0.8 (0.8 to 0.8)	1.0 (0.9 to 4.6)

End point values	Total (ALCL): 165 mg/m ² BID and 280 mg/m ² BID	Total (IMT): 165 mg/m ² BID and 280 mg/m ² BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	12		
Units: months				
median (full range (min-max))	0.9 (0.8 to 2.1)	1.0 (0.8 to 4.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anaplastic Lymphoma Kinase (ALK)-Positive Status in Pediatric Subjects with IMT or ALCL

End point title	Anaplastic Lymphoma Kinase (ALK)-Positive Status in Pediatric Subjects with IMT or ALCL
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End point description:

Subjects were considered ALK-positive based on indication of ALK abnormality and/or proven ALK-positive disease. Data was presented on the safety analysis set which included all enrolled subjects who received at least one dose of crizotinib and accounted for all IMT and ALCL pediatric subjects.

End point type	Secondary
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End point timeframe:

From baseline up to 88.8 months

End point values	ALCL: Crizotinib 165 mg/m ² BID	ALCL: Crizotinib 280 mg/m ² BID	IMT: Crizotinib 100 mg/m ² BID	IMT: Crizotinib 165 mg/m ² BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	20	1	1
Units: subjects				
number (not applicable)	6	16	1	1

End point values	IMT: Crizotinib 280 mg/m ² BID			
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Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: subjects				
number (not applicable)	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of Nucleophosmin-Anaplastic Lymphoma Kinase (NPM-ALK) in Peripheral Blood by Visit, Dose Level in ALK-positive ALCL Subjects

End point title	Levels of Nucleophosmin-Anaplastic Lymphoma Kinase (NPM-ALK) in Peripheral Blood by Visit, Dose Level in ALK-positive ALCL Subjects
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End point description:

In subjects with ALCL, peripheral blood samples were collected at baseline and following treatment at protocol specified time-points. Biomarker analysis set included all randomised subjects who had at least 1 dose of study drug and had at least one measure of minimal residual disease (MRD) based on peripheral blood using quantitative reverse transcription polymerase chain reaction (qRT-PCR) with a baseline measurement. Here, 99999 in data field signifies that data cannot be estimated. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint. Here 'n' signifies number of subjects evaluable at specified time points for 165 mg/m² and 280 mg/m² BID dose group, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Cycle 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 45, 48, 54

End point values	ALCL: Crizotinib 165 mg/m ² BID	ALCL: Crizotinib 280 mg/m ² BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	19		
Units: number of copies/10,000 ABL copies				
median (full range (min-max))				
Baseline (n= 4, 19)	19.00 (0 to 4126.0)	58.00 (0 to 501.0)		
Cycle 1 (n= 4, 13)	29.50 (0 to 77.0)	0 (0 to 1692.0)		
Cycle 2 (n= 3, 16)	0 (0 to 23.0)	0 (0 to 15038.0)		
Cycle 3 (n= 3, 11)	0 (0 to 8.0)	0 (0 to 5.0)		
Cycle 4 (n= 2, 9)	0 (0 to 0)	0 (0 to 5.0)		
Cycle 5 (n= 3, 7)	0 (0 to 3.0)	0 (0 to 3.0)		
Cycle 6 (n= 4, 7)	0 (0 to 3.0)	0 (0 to 33.0)		
Cycle 7 (n= 3, 4)	0 (0 to 0)	0 (0 to 0)		
Cycle 8 (n= 3, 3)	0 (0 to 0)	0 (0 to 0)		
Cycle 9 (n= 2, 5)	0 (0 to 0)	3.00 (0 to 12.0)		
Cycle 10 (n= 2, 5)	4.50 (0 to 9.0)	0 (0 to 399.0)		
Cycle 11 (n= 2, 5)	11.50 (10.0 to 13.0)	0 (0 to 12.0)		

Cycle 12 (n= 2, 4)	4.75 (0 to 9.5)	2.00 (0 to 11.0)		
Cycle 13 (n= 2, 3)	3.50 (0 to 7.0)	0 (0 to 513.0)		
Cycle 14 (n= 1, 5)	0 (0 to 0)	0 (0 to 4.0)		
Cycle 15 (n= 2, 2)	0.50 (0 to 1.0)	7.00 (0 to 14.0)		
Cycle 16 (n= 2, 3)	7.00 (3.0 to 11.0)	0 (0 to 0)		
Cycle 17 (n= 2, 3)	1.50 (0 to 3.0)	0 (0 to 6.0)		
Cycle 18 (n= 2, 3)	0.25 (0 to 0.5)	0 (0 to 0)		
Cycle 19 (n= 1, 2)	35.00 (35.00 to 35.00)	9.50 (0 to 19.0)		
Cycle 20 (n= 2, 2)	2 (0 to 4.0)	21.50 (0 to 43.0)		
Cycle 21 (n= 2, 1)	4.00 (0 to 8.0)	0 (0 to 0)		
Cycle 22 (n= 2, 1)	9.00 (0 to 18.0)	0 (0 to 0)		
Cycle 23 (n= 1, 2)	0 (0 to 0)	6.00 (0 to 12.0)		
Cycle 24 (n= 2, 0)	2.50 (0 to 5.0)	99999 (99999 to 99999)		
Cycle 25 (n= 1, 0)	202.50 (202.5 to 202.5)	99999 (99999 to 99999)		
Cycle 26 (n= 1, 0)	3.50 (3.5 to 3.5)	99999 (99999 to 99999)		
Cycle 27 (n= 1, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 28 (n= 2, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 29 (n= 2, 0)	0.50 (0 to 1.0)	99999 (99999 to 99999)		
Cycle 30 (n= 1, 0)	12.00 (12.00 to 12.00)	99999 (99999 to 99999)		
Cycle 31 (n= 2, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 32 (n= 2, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 33 (n= 2, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 34 (n= 2, 0)	11.00 (0 to 22.0)	99999 (99999 to 99999)		
Cycle 35 (n= 2, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 36 (n= 1, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 37 (n= 2, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 38 (n= 1, 0)	9.00 (9.0 to 9.0)	99999 (99999 to 99999)		
Cycle 39 (n= 1, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 40 (n= 1, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 42 (n= 1, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 45 (n= 2, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 48 (n= 1, 0)	0 (0 to 0)	99999 (99999 to 99999)		
Cycle 54 (n= 1, 0)	4.00 (4.00 to 4.00)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Taste Assessment of Crizotinib Oral Solution Using Taste Feedback Questionnaire

End point title	Taste Assessment of Crizotinib Oral Solution Using Taste Feedback Questionnaire
End point description: Only very few taste questionnaire were completed, and the information in there is mainly in the form of open text fields, therefore no formal analysis was performed.	
End point type	Secondary
End point timeframe: Weekly during Cycle 1	

End point values	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group	Phase 1 and 2: Other Tumors Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[2]	0 ^[3]	0 ^[4]	
Units: subjects				
number (not applicable)				

Notes:

[2] - Few questionnaires were completed, and no formal analysis was completed

[3] - Few questionnaires were completed, and no formal analysis was completed

[4] - Few questionnaires were completed, and no formal analysis was completed

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) All Causalities

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) All Causalities
End point description: An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Treatment-emergent were defined as events that occurred between first dose of study drug up to the end of study (88.8 months). Safety analysis set included all randomised subjects who received the study drug. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint.	
End point type	Secondary
End point timeframe: From baseline up to 88.8 months	

End point values	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group	Phase 1 and 2: Other Tumors Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	14	81	
Units: subjects				
number (not applicable)	26	14	81	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Test Abnormalities

End point title	Number of Subjects With Laboratory Test Abnormalities
End point description:	
Data for this endpoint was not reported because laboratory test abnormality have been captured under adverse event.	
End point type	Secondary
End point timeframe:	
From baseline up to 88.8 months	

End point values	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group	Phase 1 and 2: Other Tumors Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[5]	0 ^[6]	0 ^[7]	
Units: subjects				
number (not applicable)				

Notes:

[5] - Data for this endpoint is reported under adverse events

[6] - Data for this endpoint is reported under adverse events

[7] - Data for this endpoint is reported under adverse events

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Vital Signs Abnormalities

End point title	Number of Subjects With Vital Signs Abnormalities
End point description:	
Vital signs included assessment of body weight. Abnormality criteria included: increase from Baseline $\geq 7\%$ or decrease from Baseline $\geq 3.5\%$. Safety analysis set included all randomised subjects who	

received the study drug. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
From baseline up to 88.8. months	

End point values	ALCL and IMT: Crizotinib 100 mg/m ² BID	ALCL and IMT: Crizotinib 165 mg/m ² BID	ALCL and IMT: Crizotinib 280 mg/m ² BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	32	
Units: kilograms (Kg)				
number (not applicable)				
Maximum Increase from baseline $\geq 7\%$	1	6	18	
Maximum Decrease from baseline $\geq 3.5\%$	0	3	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Growth Plate Toxicity

End point title	Number of Subjects Reporting Growth Plate Toxicity
End point description:	
Number of subjects with evidence of growth plate toxicity (assessed by thickening in growth plate [a response of 'Yes']) was reported. Safety analysis set included all randomised subjects who received the study drug. Here 'Number of subjects analysed' signifies subjects evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Cycle 1, 3, 4, 5, 7, 9, 10, 15, 16, 18, 19, 21, 22, 23, 25, 29	

End point values	Phase 1 and 2: Anaplastic Large Cell Lymphoma (ALCL) Group	Phase 1 and 2: Inflammatory Myofibroblastic Tumors (IMT) Group	Phase 1 and 2: Other Tumors Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	6	16	
Units: subjects				
number (not applicable)				
Baseline	0	0	0	
Cycle 1	0	0	0	
Cycle 3	0	0	0	
Cycle 4	0	0	0	
Cycle 5	0	0	0	
Cycle 7	0	0	0	

Cycle 9	0	0	0	
Cycle 10	0	0	0	
Cycle 15	0	0	0	
Cycle 16	0	1	0	
Cycle 18	0	1	0	
Cycle 19	0	1	0	
Cycle 21	0	0	0	
Cycle 22	0	0	0	
Cycle 23	0	0	0	
Cycle 25	0	0	0	
Cycle 29	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event data was collected from Baseline up to 88.8 months

Adverse event reporting additional description:

Same event may appear as AE, Serious Adverse Events (SAE), what is presented are distinct events. Event may be serious in 1 and as non-serious in another or 1 subject may have experienced both. Due to limitation in COG AE CRF page, non-SAEs were not assessed separately and therefore overall AE's are reported under "other Adverse Events" section.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Phase 1: Crizotinib 100 mg/m ² BID
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Reporting group description:

In Phase 1, subjects received Crizotinib at a dose of 100 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Reporting group title	Phase 1: Crizotinib 130 mg/m ² BID
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Reporting group description:

In Phase 1, subjects received Crizotinib at a dose of 130 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Reporting group title	Phase 1: Crizotinib 165 mg/m ² BID
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Reporting group description:

In Phase 1, subjects received Crizotinib at a dose of 165 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Reporting group title	Phase 1: Crizotinib 215 mg/m ² BID
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Reporting group description:

In Phase 1, subjects received Crizotinib at a dose of 215 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Reporting group title	Phase 1: Crizotinib 280 mg/m ² BID
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Reporting group description:

In Phase 1, subjects received Crizotinib at a dose of 280 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Reporting group title	Phase 1: Crizotinib 365 mg/m ² BID
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Reporting group description:

In Phase 1, subjects received Crizotinib at a dose of 365 mg/m², orally twice daily until progressive disease or drug-related dose-limiting toxicity that required removal from therapy (up to 88.8 months).

Serious adverse events	Phase 1: Crizotinib 100 mg/m ² BID	Phase 1: Crizotinib 130 mg/m ² BID	Phase 1: Crizotinib 165 mg/m ² BID
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	3 / 8 (37.50%)	14 / 23 (60.87%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system neoplasm			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neoplasm progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Nephroblastoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Neuroblastoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Osteosarcoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyosarcoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Second primary malignancy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (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
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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			
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Blood creatinine abnormal				
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Blood creatinine increased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Gamma-glutamyltransferase abnormal				
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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	
Haemoglobin				
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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	
Haemoglobin decreased				
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Lymphocyte count decreased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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 abnormal				

subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (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
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	11 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (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
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
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			
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Myocarditis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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			
Cerebral haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (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

Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Febrile neutropenia			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (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
Neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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			
Cyanopsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (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
Constipation			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric fistula			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Kidney enlargement			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Chest wall abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective myositis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Lymph gland infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Obesity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Tumour lysis syndrome			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (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	Phase 1: Crizotinib 215 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID	Phase 1: Crizotinib 365 mg/m ² BID
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)	18 / 62 (29.03%)	4 / 11 (36.36%)
number of deaths (all causes)	2	2	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system neoplasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm progression			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Nephroblastoma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neuroblastoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Osteosarcoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Rhabdomyosarcoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Second primary malignancy subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Tumour pain subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Hypotension subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression alternative assessment type: Systematic subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Fatigue subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Hypoxia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (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
Pulmonary embolism			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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 failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Psychiatric disorders			

Confusional state			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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 / 11 (0.00%)	0 / 62 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine abnormal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin			

subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Lymphocyte count decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Neutrophil count abnormal			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Neutrophil count decreased			
subjects affected / exposed	3 / 11 (27.27%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	6 / 6	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
White blood cell count decreased			
subjects affected / exposed	2 / 11 (18.18%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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			

Sinus bradycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Myocarditis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Presyncope			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Seizure			

subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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			
Anemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (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
Febrile neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 11 (9.09%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Eye disorders			
Cyanopsia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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			
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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			
subjects affected / exposed	1 / 11 (9.09%)	1 / 62 (1.61%)	0 / 11 (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
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Flatulence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Ileus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	1 / 62 (1.61%)	0 / 11 (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
Gastric fistula			

subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Kidney enlargement			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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			
Bone pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Myositis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			

subjects affected / exposed	2 / 11 (18.18%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest wall abscess			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (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
Device related infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Infective myositis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Lymph gland infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Sepsis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Skin infection			

subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Varicella			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Varicella zoster virus infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Hypoalbuminaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (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
Hypokalaemia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Hypophosphataemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Obesity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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
Tumour lysis syndrome			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (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

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

Non-serious adverse events	Phase 1: Crizotinib 100 mg/m ² BID	Phase 1: Crizotinib 130 mg/m ² BID	Phase 1: Crizotinib 165 mg/m ² BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	8 / 8 (100.00%)	23 / 23 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	3
Tumour pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Flushing			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	4
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	9 / 23 (39.13%)
occurrences (all)	0	0	18
Hypotension			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	5 / 23 (21.74%)
occurrences (all)	4	1	22
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	6
Face oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	12 / 23 (52.17%)
occurrences (all)	2	3	33
Gait disturbance			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	1	1	2
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Localised oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	7
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	12
Non-cardiac chest pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	8 / 23 (34.78%)
occurrences (all)	0	1	11
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	4 / 23 (17.39%)
occurrences (all)	0	1	11
Pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	7 / 23 (30.43%)
occurrences (all)	2	0	16
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	9 / 23 (39.13%)
occurrences (all)	0	2	54
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Bronchospasm			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	2	1	0
Cough			
subjects affected / exposed	5 / 6 (83.33%)	2 / 8 (25.00%)	12 / 23 (52.17%)
occurrences (all)	5	2	62
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	7
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	0	1	3
Laryngeal inflammation			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Laryngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	6 / 23 (26.09%)
occurrences (all)	0	0	10
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	24
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	6 / 23 (26.09%)
occurrences (all)	0	0	15
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	3
Rhinitis allergic			
subjects affected / exposed	3 / 6 (50.00%)	0 / 8 (0.00%)	8 / 23 (34.78%)
occurrences (all)	3	0	11
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	16
Tachypnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	7
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	5 / 23 (21.74%)
occurrences (all)	0	1	8

Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	4 / 23 (17.39%)
occurrences (all)	0	1	4
Depression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences (all)	0	1	2
Irritability			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Suicidal ideation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 6 (83.33%)	2 / 8 (25.00%)	16 / 23 (69.57%)
occurrences (all)	7	3	65
Anion gap decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 6 (66.67%)	2 / 8 (25.00%)	16 / 23 (69.57%)
occurrences (all)	5	3	85
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	10 / 23 (43.48%)
occurrences (all)	0	3	24
Blood bilirubin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	1	0	6
Blood chloride increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	4
Blood creatinine increased			
subjects affected / exposed	3 / 6 (50.00%)	1 / 8 (12.50%)	14 / 23 (60.87%)
occurrences (all)	6	1	73
Blood urea decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Carbon dioxide increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	4 / 23 (17.39%)
occurrences (all)	1	1	33
Haemoglobin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	4
Lipase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	3 / 6 (50.00%)	4 / 8 (50.00%)	16 / 23 (69.57%)
occurrences (all)	5	9	31
Lymphocyte count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	2 / 6 (33.33%)	2 / 8 (25.00%)	15 / 23 (65.22%)
occurrences (all)	4	5	136
Neutrophil count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	3 / 6 (50.00%)	3 / 8 (37.50%)	8 / 23 (34.78%)
occurrences (all)	3	4	10
Protein total decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	1	0	10
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	12
White blood cell count decreased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	14 / 23 (60.87%)
occurrences (all)	3	4	95
White blood cell count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Joint injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Wound complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	5 / 23 (21.74%)
occurrences (all)	0	1	12
Sinus tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	6 / 23 (26.09%)
occurrences (all)	1	0	11
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	7 / 23 (30.43%)
occurrences (all)	0	0	11
Dysgeusia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Dyskinesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	13 / 23 (56.52%)
occurrences (all)	1	3	53
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences (all)	0	1	2
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	1 / 23 (4.35%)
occurrences (all)	0	2	1
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 8 (25.00%)	13 / 23 (56.52%)
occurrences (all)	4	6	46
Bone marrow failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Febrile neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 8 (0.00%) 0	3 / 23 (13.04%) 3
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Dyschromatopsia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Lacrimation increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Optic nerve disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Photophobia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	4
Photopsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences (all)	0	5	1
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	4 / 23 (17.39%)
occurrences (all)	0	3	4
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3

Vitreous floaters subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 8 (0.00%) 0	1 / 23 (4.35%) 1
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 8 (12.50%) 2	3 / 23 (13.04%) 4
Abdominal pain subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	1 / 8 (12.50%) 3	11 / 23 (47.83%) 19
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	0 / 8 (0.00%) 0	4 / 23 (17.39%) 5
Anal incontinence subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Colitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 8 (0.00%) 0	1 / 23 (4.35%) 1
Constipation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 8 (25.00%) 3	9 / 23 (39.13%) 24
Dental caries subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 4	3 / 8 (37.50%) 3	15 / 23 (65.22%) 80
Dyspepsia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 5	1 / 8 (12.50%) 1	6 / 23 (26.09%) 8
Dysphagia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 8 (12.50%) 1	1 / 23 (4.35%) 3
Flatulence			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	4 / 6 (66.67%)	5 / 8 (62.50%)	19 / 23 (82.61%)
occurrences (all)	6	6	51
Oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	5
Tooth discolouration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	3 / 6 (50.00%)	3 / 8 (37.50%)	19 / 23 (82.61%)
occurrences (all)	3	3	77
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	2	0	1
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	9

Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Onychoclasia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Onychomadesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	6
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	11 / 23 (47.83%)
occurrences (all)	1	0	22
Scab			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	1 / 23 (4.35%)
occurrences (all)	0	2	2
Urinary incontinence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	0	1	2
Urinary retention			

subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	0	1	2
Urinary tract pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	1	0	4
Back pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	2	1	2
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Exostosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	4
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Myositis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	2	0	12
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Enterocolitis infectious			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Lice infestation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lymphangitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	0	1	4
Rash pustular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2

Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	3
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	7
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	10 / 23 (43.48%)
occurrences (all)	2	1	22
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	4 / 23 (17.39%)
occurrences (all)	0	1	5
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	9 / 23 (39.13%)
occurrences (all)	0	2	24
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	2 / 8 (25.00%)	4 / 23 (17.39%)
occurrences (all)	1	3	5
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	0	1	2
Hyperglycaemia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	14 / 23 (60.87%)
occurrences (all)	3	1	50
Hyperkalaemia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	7 / 23 (30.43%)
occurrences (all)	0	1	8
Hypermagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	5 / 23 (21.74%)
occurrences (all)	0	2	8
Hypernatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	3 / 23 (13.04%)
occurrences (all)	1	0	6
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	4
Hypoalbuminaemia			
subjects affected / exposed	5 / 6 (83.33%)	2 / 8 (25.00%)	15 / 23 (65.22%)
occurrences (all)	10	4	82
Hypocalcaemia			
subjects affected / exposed	3 / 6 (50.00%)	3 / 8 (37.50%)	17 / 23 (73.91%)
occurrences (all)	8	6	57
Hypoglycaemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	4 / 23 (17.39%)
occurrences (all)	3	0	12
Hypokalaemia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 8 (25.00%)	9 / 23 (39.13%)
occurrences (all)	4	4	20
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	8 / 23 (34.78%)
occurrences (all)	0	0	10
Hyponatraemia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 8 (25.00%)	9 / 23 (39.13%)
occurrences (all)	3	3	12
Hypophosphataemia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 8 (0.00%)	7 / 23 (30.43%)
occurrences (all)	3	0	12

Non-serious adverse events	Phase 1: Crizotinib 215 mg/m ² BID	Phase 1: Crizotinib 280 mg/m ² BID	Phase 1: Crizotinib 365 mg/m ² BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	62 / 62 (100.00%)	11 / 11 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Skin papilloma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 11 (0.00%)	5 / 62 (8.06%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)	10 / 62 (16.13%)	0 / 11 (0.00%)
occurrences (all)	0	15	0
Hypotension			
subjects affected / exposed	2 / 11 (18.18%)	9 / 62 (14.52%)	0 / 11 (0.00%)
occurrences (all)	3	10	0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	1 / 11 (9.09%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	1	4	0
Face oedema			
subjects affected / exposed	1 / 11 (9.09%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	1	9	1
Fatigue			
subjects affected / exposed	8 / 11 (72.73%)	32 / 62 (51.61%)	8 / 11 (72.73%)
occurrences (all)	9	50	9

Gait disturbance			
subjects affected / exposed	0 / 11 (0.00%)	7 / 62 (11.29%)	1 / 11 (9.09%)
occurrences (all)	0	8	1
Influenza like illness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Localised oedema			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Malaise			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 11 (9.09%)	5 / 62 (8.06%)	2 / 11 (18.18%)
occurrences (all)	1	7	2
Oedema peripheral			
subjects affected / exposed	1 / 11 (9.09%)	9 / 62 (14.52%)	0 / 11 (0.00%)
occurrences (all)	1	23	0
Pain			
subjects affected / exposed	1 / 11 (9.09%)	16 / 62 (25.81%)	2 / 11 (18.18%)
occurrences (all)	2	19	2
Pyrexia			
subjects affected / exposed	4 / 11 (36.36%)	30 / 62 (48.39%)	1 / 11 (9.09%)
occurrences (all)	8	60	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Bronchospasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	3 / 11 (27.27%)	28 / 62 (45.16%)	2 / 11 (18.18%)
occurrences (all)	4	49	2
Dysphonia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	5 / 62 (8.06%)	2 / 11 (18.18%)
occurrences (all)	0	5	2
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Hypoxia			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	0	4	1
Laryngeal inflammation			
subjects affected / exposed	1 / 11 (9.09%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Laryngeal pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Nasal congestion			
subjects affected / exposed	1 / 11 (9.09%)	9 / 62 (14.52%)	0 / 11 (0.00%)
occurrences (all)	4	13	0
Oropharyngeal pain			
subjects affected / exposed	2 / 11 (18.18%)	13 / 62 (20.97%)	1 / 11 (9.09%)
occurrences (all)	5	13	1
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	5 / 62 (8.06%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Productive cough			
subjects affected / exposed	0 / 11 (0.00%)	5 / 62 (8.06%)	2 / 11 (18.18%)
occurrences (all)	0	5	3
Rhinitis allergic			
subjects affected / exposed	0 / 11 (0.00%)	8 / 62 (12.90%)	0 / 11 (0.00%)
occurrences (all)	0	9	0
Rhinorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	6 / 62 (9.68%)	0 / 11 (0.00%)
occurrences (all)	0	8	0
Tachypnoea			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 1	0 / 11 (0.00%) 0
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2	0 / 62 (0.00%) 0	0 / 11 (0.00%) 0
Wheezing subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 62 (3.23%) 2	0 / 11 (0.00%) 0
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	6 / 62 (9.68%) 6	1 / 11 (9.09%) 1
Anxiety subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	4 / 62 (6.45%) 5	2 / 11 (18.18%) 2
Depression subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	2 / 62 (3.23%) 2	1 / 11 (9.09%) 1
Insomnia subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	3 / 62 (4.84%) 10	1 / 11 (9.09%) 2
Irritability subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	3 / 62 (4.84%) 3	2 / 11 (18.18%) 2
Suicidal ideation subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 1	0 / 11 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	9 / 11 (81.82%) 14	50 / 62 (80.65%) 94	8 / 11 (72.73%) 15
Anion gap decreased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 2	0 / 11 (0.00%) 0
Aspartate aminotransferase increased			

subjects affected / exposed	10 / 11 (90.91%)	45 / 62 (72.58%)	9 / 11 (81.82%)
occurrences (all)	21	94	17
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 11 (27.27%)	11 / 62 (17.74%)	3 / 11 (27.27%)
occurrences (all)	12	35	4
Blood bilirubin decreased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Blood bilirubin increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Blood chloride increased			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	0	7	0
Blood cholesterol increased			
subjects affected / exposed	2 / 11 (18.18%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	2	3	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Blood creatinine increased			
subjects affected / exposed	4 / 11 (36.36%)	27 / 62 (43.55%)	6 / 11 (54.55%)
occurrences (all)	17	81	8
Blood urea decreased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
C-reactive protein increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	8	0
Carbon dioxide increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Ejection fraction decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	3 / 62 (4.84%) 3	0 / 11 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	6 / 62 (9.68%) 9	3 / 11 (27.27%) 4
Haemoglobin increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 1	0 / 11 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	3 / 62 (4.84%) 3	1 / 11 (9.09%) 1
Lymphocyte count decreased subjects affected / exposed occurrences (all)	6 / 11 (54.55%) 11	33 / 62 (53.23%) 77	5 / 11 (45.45%) 7
Lymphocyte count increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	3 / 62 (4.84%) 13	0 / 11 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	7 / 11 (63.64%) 19	51 / 62 (82.26%) 189	8 / 11 (72.73%) 17
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 62 (3.23%) 8	0 / 11 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3	12 / 62 (19.35%) 16	0 / 11 (0.00%) 0
Protein total decreased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	4 / 62 (6.45%) 12	0 / 11 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 4	6 / 62 (9.68%) 7	1 / 11 (9.09%) 1
Weight increased			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	9 / 62 (14.52%) 13	0 / 11 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	6 / 11 (54.55%) 19	42 / 62 (67.74%) 126	8 / 11 (72.73%) 17
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 6	0 / 11 (0.00%) 0
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 1	0 / 11 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 62 (1.61%) 1	2 / 11 (18.18%) 2
Fall subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 62 (6.45%) 4	0 / 11 (0.00%) 0
Fracture subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	6 / 62 (9.68%) 6	0 / 11 (0.00%) 0
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 62 (3.23%) 3	0 / 11 (0.00%) 0
Joint injury subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 1	0 / 11 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 1	0 / 11 (0.00%) 0
Wound complication subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 62 (1.61%) 1	0 / 11 (0.00%) 0
Cardiac disorders			

Myocarditis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	1 / 11 (9.09%)	8 / 62 (12.90%)	1 / 11 (9.09%)
occurrences (all)	2	10	1
Sinus tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	0	4	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 11 (18.18%)	11 / 62 (17.74%)	2 / 11 (18.18%)
occurrences (all)	3	12	3
Dysgeusia			
subjects affected / exposed	2 / 11 (18.18%)	10 / 62 (16.13%)	2 / 11 (18.18%)
occurrences (all)	3	10	2
Dyskinesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	5 / 11 (45.45%)	19 / 62 (30.65%)	3 / 11 (27.27%)
occurrences (all)	5	30	4
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 11 (9.09%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	1	5	0
Seizure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	7 / 11 (63.64%)	33 / 62 (53.23%)	9 / 11 (81.82%)
occurrences (all)	18	73	11
Bone marrow failure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dyschromatopsia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	2 / 11 (18.18%)
occurrences (all)	0	4	2
Lacrimation increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Optic nerve disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Periorbital oedema			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Photophobia			

subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	0	4	1
Photopsia			
subjects affected / exposed	2 / 11 (18.18%)	7 / 62 (11.29%)	0 / 11 (0.00%)
occurrences (all)	2	8	0
Vision blurred			
subjects affected / exposed	3 / 11 (27.27%)	18 / 62 (29.03%)	2 / 11 (18.18%)
occurrences (all)	3	21	2
Visual impairment			
subjects affected / exposed	1 / 11 (9.09%)	9 / 62 (14.52%)	2 / 11 (18.18%)
occurrences (all)	1	10	2
Vitreous floaters			
subjects affected / exposed	0 / 11 (0.00%)	6 / 62 (9.68%)	3 / 11 (27.27%)
occurrences (all)	0	11	3
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)	7 / 62 (11.29%)	2 / 11 (18.18%)
occurrences (all)	0	10	2
Abdominal pain			
subjects affected / exposed	2 / 11 (18.18%)	24 / 62 (38.71%)	2 / 11 (18.18%)
occurrences (all)	2	34	4
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	7 / 62 (11.29%)	3 / 11 (27.27%)
occurrences (all)	0	7	3
Anal incontinence			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Colitis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	5 / 11 (45.45%)	20 / 62 (32.26%)	3 / 11 (27.27%)
occurrences (all)	5	27	3
Dental caries			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0

Diarrhoea			
subjects affected / exposed	6 / 11 (54.55%)	46 / 62 (74.19%)	9 / 11 (81.82%)
occurrences (all)	20	80	13
Dyspepsia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	1	3	0
Dysphagia			
subjects affected / exposed	0 / 11 (0.00%)	5 / 62 (8.06%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Flatulence			
subjects affected / exposed	2 / 11 (18.18%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	3	4	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Nausea			
subjects affected / exposed	9 / 11 (81.82%)	41 / 62 (66.13%)	9 / 11 (81.82%)
occurrences (all)	15	87	12
Oesophagitis			
subjects affected / exposed	1 / 11 (9.09%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	1	4	1
Oral pain			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	0	4	1
Stomatitis			
subjects affected / exposed	1 / 11 (9.09%)	5 / 62 (8.06%)	0 / 11 (0.00%)
occurrences (all)	1	5	0
Tooth discolouration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Vomiting			
subjects affected / exposed	8 / 11 (72.73%)	48 / 62 (77.42%)	11 / 11 (100.00%)
occurrences (all)	17	144	16

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Dermatitis acneiform			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	1 / 11 (9.09%)
occurrences (all)	0	3	1
Dry skin			
subjects affected / exposed	1 / 11 (9.09%)	5 / 62 (8.06%)	1 / 11 (9.09%)
occurrences (all)	3	6	2
Erythema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Onychoclasia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Onychomadesis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)	10 / 62 (16.13%)	1 / 11 (9.09%)
occurrences (all)	1	11	1
Rash			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 11 (0.00%)	6 / 62 (9.68%)	0 / 11 (0.00%)
occurrences (all)	0	12	0
Scab			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Haematuria			

subjects affected / exposed	1 / 11 (9.09%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	1	3	0
Proteinuria			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Urinary incontinence			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Urinary retention			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Urinary tract pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Back pain			
subjects affected / exposed	2 / 11 (18.18%)	6 / 62 (9.68%)	3 / 11 (27.27%)
occurrences (all)	2	9	3
Bone pain			
subjects affected / exposed	1 / 11 (9.09%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	1	3	0
Exostosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Myalgia			

subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Myositis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	1 / 11 (9.09%)
occurrences (all)	0	1	2
Pain in extremity			
subjects affected / exposed	2 / 11 (18.18%)	22 / 62 (35.48%)	3 / 11 (27.27%)
occurrences (all)	6	31	3
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Enterocolitis infectious			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Gastroenteritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Lice infestation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Lymphangitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	0	6	1
Paronychia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	4	0

Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Rash pustular			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	1	3	0
Skin infection			
subjects affected / exposed	2 / 11 (18.18%)	6 / 62 (9.68%)	0 / 11 (0.00%)
occurrences (all)	2	14	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	13 / 62 (20.97%)	1 / 11 (9.09%)
occurrences (all)	1	14	1
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 62 (3.23%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 62 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	5 / 11 (45.45%)	26 / 62 (41.94%)	7 / 11 (63.64%)
occurrences (all)	6	33	7
Dehydration			

subjects affected / exposed	1 / 11 (9.09%)	4 / 62 (6.45%)	2 / 11 (18.18%)
occurrences (all)	1	4	2
Hypercalcaemia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 62 (4.84%)	1 / 11 (9.09%)
occurrences (all)	0	15	1
Hyperglycaemia			
subjects affected / exposed	4 / 11 (36.36%)	30 / 62 (48.39%)	5 / 11 (45.45%)
occurrences (all)	10	42	9
Hyperkalaemia			
subjects affected / exposed	3 / 11 (27.27%)	14 / 62 (22.58%)	0 / 11 (0.00%)
occurrences (all)	5	20	0
Hypermagnesaemia			
subjects affected / exposed	4 / 11 (36.36%)	19 / 62 (30.65%)	3 / 11 (27.27%)
occurrences (all)	5	30	4
Hypernatraemia			
subjects affected / exposed	1 / 11 (9.09%)	10 / 62 (16.13%)	1 / 11 (9.09%)
occurrences (all)	1	16	1
Hyperphosphataemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 62 (1.61%)	0 / 11 (0.00%)
occurrences (all)	0	9	0
Hyperuricaemia			
subjects affected / exposed	0 / 11 (0.00%)	4 / 62 (6.45%)	1 / 11 (9.09%)
occurrences (all)	0	6	2
Hypoalbuminaemia			
subjects affected / exposed	5 / 11 (45.45%)	36 / 62 (58.06%)	5 / 11 (45.45%)
occurrences (all)	21	86	6
Hypocalcaemia			
subjects affected / exposed	8 / 11 (72.73%)	32 / 62 (51.61%)	5 / 11 (45.45%)
occurrences (all)	21	73	5
Hypoglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	21 / 62 (33.87%)	4 / 11 (36.36%)
occurrences (all)	13	32	6
Hypokalaemia			
subjects affected / exposed	4 / 11 (36.36%)	12 / 62 (19.35%)	4 / 11 (36.36%)
occurrences (all)	10	15	4
Hypomagnesaemia			

subjects affected / exposed	0 / 11 (0.00%)	9 / 62 (14.52%)	1 / 11 (9.09%)
occurrences (all)	0	11	1
Hyponatraemia			
subjects affected / exposed	0 / 11 (0.00%)	13 / 62 (20.97%)	1 / 11 (9.09%)
occurrences (all)	0	16	1
Hypophosphataemia			
subjects affected / exposed	6 / 11 (54.55%)	14 / 62 (22.58%)	5 / 11 (45.45%)
occurrences (all)	17	20	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2017	Pfizer is not the Sponsor and cannot provide details of substantial changes. The final protocol amendment is available here https://clinicaltrials.gov/ProvidedDocs/70/NCT00939770/Prot_SAP_ICF_001.pdf

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported