

**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 |
|-----------------------|----------|

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 |
|-------------------|---|

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 |
|------------------|--|

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 |
|------------------|-----------------------------------|

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 |
|-----------------------|--|

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 |
|-----------------------|--|

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 |
|-----------------------|-----------------------------------|

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] |
|-----------------|--|

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 |
|----------------|---------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|-----------------|---|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 | 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 |
|-----------------|---|

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 |
|----------------|-----------|

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) |
|-----------------|---|

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 |
|----------------|-----------|

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) |
|-----------------|---|

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 |
|----------------|-----------|

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) |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 | | | |
|------------------|---|--|--|--|
|------------------|---|--|--|--|

| | | | | |
|-----------------------------|----------------------|--|--|--|
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

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

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 |
|-----------------------|---|

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 |
|-----------------------|---|

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 |
|-----------------------|---|

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 |
|-----------------------|---|

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 |
|-----------------------|---|

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 |
| Gastroesophageal 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