



Clinical trial results:

PHASE 1B OPEN-LABEL STUDY OF THE SAFETY AND CLINICAL ACTIVITY OF CRIZOTINIB (PF-02341066) IN TUMORS WITH GENETIC EVENTS INVOLVING THE ANAPLASTIC LYMPHOMA KINASE (ALK) GENE LOCUS

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2010-022978-14 |
| Trial protocol | IT Outside EU/EEA |
| Global end of trial date | 07 September 2023 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 March 2024 |
| First version publication date | 15 March 2024 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A8081013 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01121588 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, |
| Public contact | Pfizer ClinicalTrials.gov Call Center , Pfizer, Inc. , +1 18007181021, |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center , Pfizer, Inc. , +1 18007181021, |

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 | 07 September 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 September 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 September 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 1 trial evaluating the safety and efficacy of crizotinib in patients with tumors except non-small cell lung cancer that are positive for ALK.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 22 March 2011 |
| 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 | China: 8 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Japan: 5 |
| Country: Number of subjects enrolled | Korea, Republic of: 7 |
| Country: Number of subjects enrolled | Russian Federation: 4 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Country: Number of subjects enrolled | United States: 7 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 12 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 5 |
| Adults (18-64 years) | 35 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 44 Anaplastic lymphoma kinase (ALK) genetic event positive subjects were enrolled into the study: 17 with anaplastic large cell lymphoma (ALCL), 9 with inflammatory myofibroblastic tumors (IMT), and 18 with other tumors (ALK-positive malignancies excluding nonsmall cell lung cancer).

Pre-assignment

Screening details:

A total of 44 Anaplastic lymphoma kinase (ALK) genetic event positive subjects were enrolled into the study: 17 with anaplastic large cell lymphoma (ALCL), 9 with inflammatory myofibroblastic tumors (IMT), and 18 with other tumors (ALK-positive malignancies excluding nonsmall cell lung cancer). All subjects discontinued study.

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 | Anaplastic Large Cell Lymphoma (ALCL) |

Arm description:

In ALK genetic event positive subjects with ALCL, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

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

Dosage and administration details:

Crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods.

| | |
|------------------|---|
| Arm title | Inflammatory Myofibroblastic Tumors (IMT) |
|------------------|---|

Arm description:

In ALK genetic event positive subjects with IMT, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

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

Dosage and administration details:

Crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles

were defined in 21 day periods.

| | |
|------------------|--------------|
| Arm title | Other Tumors |
|------------------|--------------|

Arm description:

In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

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

Dosage and administration details:

Crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods.

| Number of subjects in period 1 | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors |
|----------------------------------|---------------------------------------|---|--------------|
| | | | |
| Started | 17 | 9 | 18 |
| Completed | 0 | 0 | 0 |
| Not completed | 17 | 9 | 18 |
| Adverse event, serious fatal | 5 | 3 | 13 |
| Non-Specified Reasons | 9 | 4 | 2 |
| Subject Refused Further Followup | 2 | - | 2 |
| Study Terminated by Sponsor | 1 | 1 | - |
| Lost to follow-up | - | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Anaplastic Large Cell Lymphoma (ALCL) |
|-----------------------|---------------------------------------|

Reporting group description:

In ALK genetic event positive subjects with ALCL, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

| | |
|-----------------------|---|
| Reporting group title | Inflammatory Myofibroblastic Tumors (IMT) |
|-----------------------|---|

Reporting group description:

In ALK genetic event positive subjects with IMT, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

| | |
|-----------------------|--------------|
| Reporting group title | Other Tumors |
|-----------------------|--------------|

Reporting group description:

In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

| Reporting group values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors |
|---|---------------------------------------|---|--------------|
| Number of subjects | 17 | 9 | 18 |
| Age Categorical Units: Subjects | | | |
| <18 years | 3 | 2 | 0 |
| Between 18 and 65 years | 14 | 6 | 15 |
| >=65 years | 0 | 1 | 3 |
| Age Continuous Units: Years | | | |
| median | 25.0 | 32.0 | 49.0 |
| full range (min-max) | 15.0 to 37.0 | 16.0 to 73.0 | 18.0 to 73.0 |
| Sex: Female, Male Units: Subjects | | | |
| Overall population excluding pediatric Female | 4 | 3 | 10 |
| Pediatric Population Female | 1 | 1 | 0 |
| Overall population excluding pediatric Male | 10 | 4 | 8 |
| Pediatric Population Male | 2 | 1 | 0 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White (including 1 pediatric subject with ALCL) | 12 | 4 | 7 |
| Black | 0 | 0 | 0 |
| Asian (including 2 ALCL and 2 IMT pediatric) | 5 | 5 | 11 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Age Continuous Units: Years median full range (min-max) | 25.0 15.0 to 37.0 | 32.0 16.0 to 73.0 | 49.0 18.0 to 73.0 |
| Reporting group values | Total | | |
| Number of subjects | 44 | | |
| Age Categorical Units: Subjects | | | |
| <18 years | 5 | | |
| Between 18 and 65 years | 35 | | |
| >=65 years | 4 | | |
| Age Continuous Units: Years median full range (min-max) | - | | |
| Sex: Female, Male Units: Subjects | | | |
| Overall population excluding pediatric Female | 17 | | |
| Pediatric Population Female | 2 | | |
| Overall population excluding pediatric Male | 22 | | |
| Pediatric Population Male | 3 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White (including 1 pediatric subject with ALCL) | 23 | | |
| Black | 0 | | |
| Asian (including 2 ALCL and 2 IMT pediatric) | 21 | | |
| Age Continuous Units: Years median full range (min-max) | - | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Anaplastic Large Cell Lymphoma (ALCL) |
| Reporting group description: In ALK genetic event positive subjects with ALCL, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator. | |
| Reporting group title | Inflammatory Myofibroblastic Tumors (IMT) |
| Reporting group description: In ALK genetic event positive subjects with IMT, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator. | |
| Reporting group title | Other Tumors |
| Reporting group description: In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator. | |

Primary: Number of Subjects With All-Causality Treatment-Emergent Adverse Events (TEAEs)

| | |
|--|--|
| End point title | Number of Subjects With All-Causality Treatment-Emergent Adverse Events (TEAEs) ^[1] |
| End point description: An adverse event (AE) was any untoward medical occurrence in a participant who received study treatment without regard to possibility of causal relationship. Serious adverse event (SAE) was an AE resulting in any of the following outcomes: death, initial or prolonged inpatient hospitalization, life-threatening experience, persistent or significant disability/incapacity, congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication. Grades of AEs were defined by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5= death related to AE. | |
| End point type | Primary |
| End point timeframe: From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks) | |

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: No statistical analysis was planned.

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|-----------------------------|---------------------------------------|---|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 | 9 | 18 | |
| Units: Subjects | | | | |

| | | | | |
|--|----|---|----|--|
| AEs | 17 | 9 | 17 | |
| SAEs | 8 | 4 | 7 | |
| Maximum Grade 3 or 4 AEs | 13 | 7 | 8 | |
| Maximum Grade 5 AEs | 2 | 0 | 4 | |
| AEs resulting in study trt d/c (subject continued) | 1 | 0 | 3 | |
| AEs resulting in dose reduction | 4 | 1 | 3 | |
| AEs resulting in temporary d/c of study trt | 8 | 6 | 10 | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With All-Causality TEAEs in the Pediatric Population

| | |
|-----------------|--|
| End point title | Number of Subjects With All-Causality TEAEs in the Pediatric Population ^[2] |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence in a participant An AE was any untoward medical occurrence in a participant who received study treatment without regard to possibility of causal relationship. Serious AE was an AE resulting in death, initial or prolonged inpatient hospitalization, life-threatening experience, persistent or significant disability/incapacity, congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication. Grades of AEs were defined by NCI CTCAE version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5=death related to AE.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 342 weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned.

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|--|---------------------------------------|---|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 2 | 0 ^[3] | |
| Units: Subjects | | | | |
| AEs | 3 | 2 | | |
| SAEs | 2 | 1 | | |
| Maximum Grade 3 or 4 AEs | 3 | 2 | | |
| Maximum Grade 5 AEs | 0 | 0 | | |
| AEs resulting in study trt d/c (subject continued) | 0 | 0 | | |
| AEs resulting in dose reduction | 1 | 0 | | |
| AEs resulting in temporary d/c of study trt | 2 | 2 | | |

Notes:

[3] - There was 0 pediatric subject in other tumors group

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Related TEAEs

| | |
|-----------------|--|
| End point title | Number of Subjects With Treatment-Related TEAEs ^[4] |
|-----------------|--|

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a participant who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication. Grades of AEs were defined by NCI CTCAE version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5=death related to AE.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

Notes:

[4] - 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: No statistical analysis was planned.

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|--|---------------------------------------|---|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 | 9 | 18 | |
| Units: Subjects | | | | |
| AEs | 16 | 8 | 15 | |
| SAEs | 5 | 3 | 2 | |
| Maximum Grade 3 or 4 AEs | 11 | 5 | 6 | |
| Maximum Grade 5 AEs | 0 | 0 | 2 | |
| AEs resulting in study trt d/c (subject continued) | 0 | 0 | 2 | |
| AEs resulting in doser reduction | 4 | 1 | 3 | |
| AEs resulting in temporary d/c of study trt | 6 | 4 | 6 | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Related TEAEs in the Pediatric

Population

| | |
|-----------------|--|
| End point title | Number of Subjects With Treatment-Related TEAEs in the Pediatric Population ^[5] |
|-----------------|--|

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a participant who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication. Grades of AEs were defined by NCI CTCAE version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5=death related to AE.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 342 weeks)

Notes:

[5] - 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: No statistical analysis was planned.

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|--|---------------------------------------|---|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 2 | 0 ^[6] | |
| Units: Subjects | | | | |
| AEs | 3 | 2 | | |
| SAEs | 2 | 1 | | |
| Maximum Grade 3 or 4 AEs | 2 | 1 | | |
| Maximum Grade 5 AEs | 0 | 0 | | |
| AEs resulting in study trt d/c (subject continued) | 0 | 0 | | |
| AEs resulting in dose reduction | 1 | 0 | | |
| AEs resulting in temporary d/c of study trt | 1 | 1 | | |

Notes:

[6] - Zero pediatric subject in other tumors group was reported for this endpoint

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Laboratory Test Results Shifted From Grade ≤2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries)

| | |
|-----------------|--|
| End point title | Number of Subjects With Laboratory Test Results Shifted From Grade ≤2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries) ^[7] |
|-----------------|--|

End point description:

Baseline assessment was defined as the last assessment performed on or prior to the date of the first dose of study treatment. Both hematology and chemistry laboratory assessments were analyzed. Grades of severity were defined by CTCAE v4.0. Grade 2 = moderate adverse event; Grade 3= severe adverse event; Grade 4 = life-threatening consequences; urgent intervention indicated.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

Notes:

[7] - 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: No statistical analysis was planned.

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|--------------------------------------|---------------------------------------|---|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 9 | 16 | |
| Units: Subjects | | | | |
| Anemia | 1 | 0 | 5 | |
| Hemoglobin increased | 0 | 0 | 0 | |
| Lymphocyte count decreased | 1 | 1 | 4 | |
| Lymphocyte count increased | 0 | 0 | 0 | |
| Neutrophil count decreased | 8 | 3 | 1 | |
| Platelet count decreased | 0 | 0 | 0 | |
| White blood cell decreased | 3 | 0 | 1 | |
| Alanine aminotransferase increased | 2 | 1 | 2 | |
| Alkaline phosphatase increased | 0 | 0 | 0 | |
| Aspartate aminotransferase increased | 4 | 0 | 1 | |
| Blood bilirubin increased | 0 | 0 | 1 | |
| Creatinine increased | 0 | 0 | 0 | |
| Hypercalcemia | 0 | 0 | 0 | |
| Hyperglycemia | 0 | 0 | 0 | |
| Hyperkalemia | 2 | 0 | 0 | |
| Hypermagnesemia | 0 | 0 | 1 | |
| Hypernatremia | 0 | 0 | 0 | |
| Hypoalbuminemia | 0 | 0 | 2 | |
| Hypocalcemia | 0 | 0 | 0 | |
| Hypoglycemia | 2 | 0 | 0 | |
| Hypokalemia | 0 | 0 | 2 | |
| Hypomagnesemia | 0 | 0 | 0 | |
| Hyponatremia | 0 | 0 | 2 | |
| Hypophosphatemia | 3 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Laboratory Test Results Shifted From Grade ≤2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries) in the Pediatric Population

| | |
|-----------------|--|
| End point title | Number of Subjects With Laboratory Test Results Shifted From Grade ≤2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries) in the Pediatric Population ^[8] |
|-----------------|--|

End point description:

Baseline assessment was defined as the last assessment performed on or prior to the date of the first

dose of study treatment. Both hematology and chemistry laboratory assessments were analyzed. Grades of severity were defined by CTCAE v4.0. Grade 2 = moderate adverse event; Grade 3 = severe adverse event; Grade 4 = life-threatening consequences; urgent intervention indicated. Unplanned laboratory test results were also included.

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 342 weeks) | |

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned.

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|--------------------------------------|---------------------------------------|---|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 2 | 0 ^[9] | |
| Units: Subjects | | | | |
| Anemia | 0 | 0 | | |
| Hemoglobin increased | 0 | 0 | | |
| Lymphocyte count decreased | 1 | 0 | | |
| Lymphocyte count increased | 0 | 0 | | |
| Neutrophil count decreased | 2 | 1 | | |
| Platelet count decreased | 0 | 0 | | |
| White blood cell decreased | 2 | 0 | | |
| Alanine aminotransferase increased | 0 | 0 | | |
| Alkaline phosphatase increased | 0 | 0 | | |
| Aspartate aminotransferase increased | 1 | 0 | | |
| Blood bilirubin increased | 0 | 0 | | |
| Creatinine increased | 0 | 0 | | |
| Hypercalcemia | 0 | 0 | | |
| Hyperglycemia | 0 | 0 | | |
| Hyperkalemia | 0 | 0 | | |
| Hypermagnesemia | 0 | 0 | | |
| Hypernatremia | 0 | 0 | | |
| Hypoalbuminemia | 0 | 0 | | |
| Hypocalcemia | 0 | 0 | | |
| Hypoglycemia | 1 | 0 | | |
| Hypokalemia | 0 | 0 | | |
| Hypomagnesemia | 0 | 0 | | |
| Hyponatremia | 0 | 0 | | |
| Hypophosphatemia | 1 | 0 | | |

Notes:

[9] - There was 0 pediatric subject in other tumors group

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) - Percentage of Subjects With Objective Response

| | |
|-----------------|---|
| End point title | Objective Response Rate (ORR) - Percentage of Subjects With |
|-----------------|---|

End point description:

Percentage of participants with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) (1.1) as determined by the investigators. CR = disappearance of all target lesions. PR = greater than equal to (\geq) 30% decrease in sum of target lesions taking as reference baseline sum diameters. ORR based on Cheson criteria was defined similarly however, confirmation of response was not required. If participant had tumor response assessed only by RECIST or Cheson, then ORR was based on the single result. If tumor response was assessed by both RECIST and Cheson, then ORR was reported based on tumor response by Cheson criteria unless the Cheson has indeterminate result, in which case the RECIST result was reported. Participant(s) who did not have tumor assessment results from either RECIST 1.1 or Cheson criteria reported at baseline were to be excluded from the analysis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the date of first dose of study medication to the date of the first documentation of objective tumor progression or death on treatment due to any cause, whichever occurred first (maximum 374 weeks)

Notes:

[10] - 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: No statistical analysis was planned.

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|----------------------------------|---------------------------------------|---|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 9 | 18 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 56.3 (33.2 to 76.9) | 66.7 (35.4 to 87.9) | 16.7 (5.8 to 39.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Based on Investigator Assessment

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) Based on Investigator Assessment |
|-----------------|--|

End point description:

PFS was defined as the time from the date of first dose of study medication to the date of the first documentation of objective tumor progression (at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study [this includes the baseline sum if that is the smallest on study]). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression) or death on treatment due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. The median PFS was estimated using Kaplan-Meier method.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of first dose of study medication to the date of the first documentation of objective tumor progression or death on treatment due to any cause, whichever occurs first (maximum 444 weeks)

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|----------------------------------|---------------------------------------|---|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 ^[11] | 9 ^[12] | 18 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (2.1 to 99999) | 99999 (11.1 to 99999) | 1.4 (1.1 to 4.9) | |

Notes:

[11] - Median PFD and upper limit of CI not estimable due to insufficient number of subjects with event.

[12] - Median PFD and upper limit of CI not estimable due to insufficient number of subjects with event.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Surviving at 6 Months and 1 Year

| | |
|--|---|
| End point title | Percentage of Participants Surviving at 6 Months and 1 Year |
| End point description: | |
| The probability of survival at 6 months and 1 year, respectively, after the date of the first dose based on the Kaplan-Meier estimate. | |
| End point type | Secondary |
| End point timeframe: | |
| At 6 months and 1 year after first dose | |

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|----------------------------------|---------------------------------------|---|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 | 9 | 18 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 6 Months | 76.5 (48.8 to 90.4) | 100.0 (100.0 to 100.0) | 52.9 (27.6 to 73.0) | |
| 1 Year | 70.6 (43.1 to 86.6) | 100.0 (100.0 to 100.0) | 52.9 (27.6 to 73.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS is defined as the time from the date of first dose of study medication to the date of death due to any cause. OS (in months) was calculated as (date of death – date of first dose +1)/30.42. For subjects still alive at the time of the analysis, for those who were lost to follow-up, and those who withdrew consent for additional follow up, the OS was censored on the last date that participants were known to be alive. Subjects lacking data beyond the first dose had their OS censored at the date of first dose. The median | |

OS was estimated using Kaplan-Meier method.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the first dose of study treatment to the date of death due to any cause (maximum 444 weeks) | |

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|----------------------------------|---------------------------------------|---|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 17 ^[13] | 9 ^[14] | 18 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (7.5 to 99999) | 99999 (32.1 to 99999) | 12.6 (2.2 to 27.0) | |

Notes:

[13] - Median OS and upper limit of CI not estimable due to insufficient number of subjects with event.

[14] - Median OS and upper limit of CI not estimable due to insufficient number of subjects with event.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) Based on Investigator Assessment

| | |
|-----------------|--|
| End point title | Duration of Response (DR) Based on Investigator Assessment |
|-----------------|--|

End point description:

DR was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. CR: disappearance of all lesions; any pathological lymph nodes (target lesions [TLs]) or non-target lesions (non-TLs) must have reduction in short axis to <10 mm; normalization of tumor marker level for non-TLs; PR: $\geq 30\%$ decrease in sum of diameter of all TLs, taking as reference baseline sum of diameters; DR (in weeks) was calculated as (first date of PD or death – first date of CR or PR +1)/7. The median DR was estimated using Kaplan-Meier estimates.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first (maximum 374 weeks)

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|----------------------------------|---------------------------------------|---|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 ^[15] | 6 ^[16] | 3 ^[17] | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (30.1 to 9999) | 9999 (16.1 to 9999) | |

Notes:

[15] - This is showing DR for the patients without subsequent progression or death

[16] - This is showing DR for the patients without subsequent progression or death

[17] - This is showing DR for the patients without subsequent progression or death

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Pre-dose Concentration (Ctough) for Crizotinib on Day 1 of Cycles 2, 3 and 5

| | |
|-----------------|---|
| End point title | Steady-State Pre-dose Concentration (Ctough) for Crizotinib on Day 1 of Cycles 2, 3 and 5 |
|-----------------|---|

End point description:

Ctough is defined as the drug concentration observed at the last planned timepoint prior to dosing. Steady state is defined as the subject receiving at least 90% of Crizotinib 500 mg daily dosing 14 days prior to the PK sample collection.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose within 1.2 hours before dosing on Day 1 of Cycles 2, 3 and 5

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|---|---------------------------------------|---|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 8 | 12 | |
| Units: nanogram per millilitre (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 2 Day 1 | 270 (± 46.2) | 266 (± 42.0) | 233 (± 101) | |
| Cycle 3 Day 1 | 316 (± 33.4) | 179 (± 92.1) | 187 (± 224) | |
| Cycle 5 Day 1 | 244 (± 80.0) | 257 (± 35.1) | 347 (± 63.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Ctough for PF-06260182 on Day 1 of Cycles 2, 3 and 5

| | |
|-----------------|---|
| End point title | Steady-State Ctough for PF-06260182 on Day 1 of Cycles 2, 3 and 5 |
|-----------------|---|

End point description:

Ctough is defined as the drug concentration observed at the last planned timepoint prior to dosing. Steady state is defined as the subject receiving at least 90% of Crizotinib 500 mg daily dosing 14 days prior to the PK sample collection.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose within 1.2 hours before dosing on Day 1 of Cycles 2, 3 and 5

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|---|---------------------------------------|---|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 8 | 12 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 2 Day 1 | 79.7 (± 64.6) | 68.2 (± 56.4) | 54.6 (± 123) | |
| Cycle 3 Day 1 | 85.4 (± 88.2) | 41.7 (± 147) | 50.5 (± 566) | |
| Cycle 5 Day 1 | 81.7 (± 96.8) | 71.9 (± 48.2) | 91.7 (± 68.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough Ratios of PF-06260182 to Crizotinib on Day 1 of Cycles 2, 3 and 5

| | |
|-----------------|---|
| End point title | Ctrough Ratios of PF-06260182 to Crizotinib on Day 1 of Cycles 2, 3 and 5 |
|-----------------|---|

End point description:

Ctrough is defined as the drug concentration observed at the last planned timepoint prior to dosing. Steady state is defined as the participant receiving at least 90% of Crizotinib 500 mg daily dosing 14 days prior to the PK sample collection. The ratio is calculated as: (PF-06260182 concentration/464.33)/(Crizotinib concentration/450.34), where 464.33 is molecular weight for PF-06260182 and 450.33 is molecular weight for Crizotinib.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose within 1.2 hours before dosing on Day 1 of Cycles 2, 3 and 5

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|---|---------------------------------------|---|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 8 | 12 | |
| Units: ratio | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 2 Day 1 | 0.323 (± 15.2) | 0.249 (± 25.0) | 0.190 (± 32.7) | |
| Cycle 3 Day 1 | 0.314 (± 26.0) | 0.226 (± 41.4) | 0.126 (± 108) | |
| Cycle 5 Day 1 | 0.326 (± 28.3) | 0.270 (± 27.7) | 0.243 (± 28.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With ALK Genetic Events

| | |
|-----------------|--|
| End point title | Number of Subjects With ALK Genetic Events |
|-----------------|--|

End point description:

Planned analysis (molecular profiling results including ALK fusion/translocation, mutations, amplification and overexpression) was not performed due to insufficient samples.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|-----------------------------|---------------------------------------|---|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[18] | 0 ^[19] | 0 ^[20] | |
| Units: Subjects | | | | |

Notes:

[18] - The analysis was not performed due to insufficient samples.

[19] - The analysis was not performed due to insufficient samples.

[20] - The analysis was not performed due to insufficient samples.

Statistical analyses

No statistical analyses for this end point

Secondary: Phosphorylation Status of ALK in the Tumor Samples From Surgery or Biopsy Pre and Post Treatment

| | |
|-----------------|--|
| End point title | Phosphorylation Status of ALK in the Tumor Samples From Surgery or Biopsy Pre and Post Treatment |
|-----------------|--|

End point description:

Tumor sample was planned to be provided to the designated central laboratory for retrospective confirmation of ALK genetic event by a Pfizer designated central laboratory. The molecular profiling results were planned to include ALK fusion/translocation, mutations, amplification and overexpression. The analysis was not performed due to insufficient samples.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

| End point values | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors | |
|-----------------------------|---------------------------------------|---|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[21] | 0 ^[22] | 0 ^[23] | |
| Units: Subjects | | | | |

Notes:

[21] - The analysis was not performed due to insufficient samples.

[22] - The analysis was not performed due to insufficient samples.

[23] - The analysis was not performed due to insufficient samples.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum duration between first and last dose: 604.1 weeks)

Adverse event reporting additional description:

Same event may appear as non-SAE and SAE; however, what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during the study.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Anaplastic Large Cell Lymphoma (ALCL) |
|-----------------------|---------------------------------------|

Reporting group description:

In ALK genetic event positive subjects with ALCL, crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

| | |
|-----------------------|---|
| Reporting group title | Inflammatory Myofibroblastic Tumors (IMT) |
|-----------------------|---|

Reporting group description:

In ALK genetic event positive subjects with IMT, crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

| | |
|-----------------------|--------------|
| Reporting group title | Other Tumors |
|-----------------------|--------------|

Reporting group description:

In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

| Serious adverse events | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors |
|---|---------------------------------------|---|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 17 (47.06%) | 4 / 9 (44.44%) | 7 / 18 (38.89%) |
| number of deaths (all causes) | 5 | 3 | 13 |
| number of deaths resulting from adverse events | 3 | 0 | 4 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (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 |

| | | | |
|--|-----------------|----------------|----------------|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (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 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (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 |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Eye disorders | | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (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 |
| Eyelid ptosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (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 |
| Faecaloma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| 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 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Neurogenic bladder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Sepsis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| 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 | | | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 | Anaplastic Large Cell Lymphoma (ALCL) | Inflammatory Myofibroblastic Tumors (IMT) | Other Tumors |
|---|---------------------------------------|---|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 17 (94.12%) | 9 / 9 (100.00%) | 17 / 18 (94.44%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Varicose vein | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Peripheral coldness | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Surgical and medical procedures | | | |
| Abscess drainage | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Mole excision | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 7 / 17 (41.18%) | 0 / 9 (0.00%) | 2 / 18 (11.11%) |
| occurrences (all) | 10 | 0 | 2 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 2 / 18 (11.11%) |
| occurrences (all) | 0 | 1 | 2 |
| Chest pain | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 2 | 0 | 1 |
| Cyst | | | |

| | | | |
|-----------------------------|------------------|----------------|-----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 1 / 9 (11.11%) | 5 / 18 (27.78%) |
| occurrences (all) | 5 | 1 | 9 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 3 / 9 (33.33%) | 6 / 18 (33.33%) |
| occurrences (all) | 28 | 6 | 10 |
| Pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 2 | 0 | 1 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 17 (58.82%) | 1 / 9 (11.11%) | 2 / 18 (11.11%) |
| occurrences (all) | 18 | 1 | 2 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Immune system disorders | | | |

| | | | |
|---|----------------------|---------------------|----------------------|
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Erectile dysfunction subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Intermenstrual bleeding subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Ovarian cyst subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Vaginal discharge subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 3 / 17 (17.65%) 4 | 1 / 9 (11.11%) 5 | 4 / 18 (22.22%) 6 |
| Atelectasis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Cough subjects affected / exposed occurrences (all) | 7 / 17 (41.18%) 9 | 1 / 9 (11.11%) 1 | 4 / 18 (22.22%) 4 |
| Pharyngeal erythema subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Paranasal cyst | | | |

| | | | |
|------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 1 / 18 (5.56%) |
| occurrences (all) | 2 | 1 | 3 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 9 (11.11%) | 1 / 18 (5.56%) |
| occurrences (all) | 5 | 3 | 1 |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |

| | | | |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 2 / 18 (11.11%) |
| occurrences (all) | 0 | 3 | 2 |
| Aggression | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 2 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 2 / 18 (11.11%) |
| occurrences (all) | 1 | 0 | 3 |
| Libido decreased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 3 |
| Investigations | | | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 17 (52.94%) | 4 / 9 (44.44%) | 5 / 18 (27.78%) |
| occurrences (all) | 53 | 26 | 12 |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|------------------|----------------|-----------------|
| subjects affected / exposed | 10 / 17 (58.82%) | 4 / 9 (44.44%) | 6 / 18 (33.33%) |
| occurrences (all) | 34 | 20 | 12 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 9 (22.22%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 2 | 4 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 2 / 18 (11.11%) |
| occurrences (all) | 1 | 0 | 2 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 2 / 9 (22.22%) | 0 / 18 (0.00%) |
| occurrences (all) | 38 | 3 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 2 / 9 (22.22%) | 1 / 18 (5.56%) |
| occurrences (all) | 5 | 2 | 1 |
| Blood folate decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood testosterone decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |

| | | | |
|-------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 1 / 18 (5.56%) |
| occurrences (all) | 1 | 1 | 1 |
| Globulins decreased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 2 / 18 (11.11%) |
| occurrences (all) | 0 | 0 | 2 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 6 | 2 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 2 / 9 (22.22%) | 1 / 18 (5.56%) |
| occurrences (all) | 61 | 3 | 6 |

| | | | |
|--|-----------------|----------------|----------------|
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 3 | 0 | 1 |
| Contusion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Exposure during pregnancy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Paternal exposure during pregnancy | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |

| | | | |
|---|----------------------|---------------------|----------------------|
| Gilbert's syndrome subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Cardiac disorders | | | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 18 (0.00%) 0 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Memory impairment subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 6 / 17 (35.29%) 7 | 1 / 9 (11.11%) 1 | 2 / 18 (11.11%) 2 |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Dysaesthesia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 18 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 1 / 9 (11.11%) 1 | 1 / 18 (5.56%) 1 |
| Amnesia | | | |

| | | | |
|--------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ageusia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Petit mal epilepsy | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Visual perseveration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Tremor | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Taste disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 2 / 18 (11.11%) |
| occurrences (all) | 0 | 3 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 9 (22.22%) | 6 / 18 (33.33%) |
| occurrences (all) | 8 | 6 | 7 |
| Lymph node pain | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Lymphoid tissue hyperplasia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 9 (11.11%) | 1 / 18 (5.56%) |
| occurrences (all) | 33 | 8 | 16 |
| Myelosuppression | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 7 / 17 (41.18%) | 4 / 9 (44.44%) | 3 / 18 (16.67%) |
| occurrences (all) | 75 | 28 | 9 |

| | | | |
|--|----------------------|---------------------|-----------------------|
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 3 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 2 |
| Leukopenia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 4 | 2 / 9 (22.22%) 4 | 2 / 18 (11.11%) 11 |
| Ear and labyrinth disorders | | | |
| Ear discomfort subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Otorrhoea subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Eye disorders | | | |
| Conjunctivitis allergic subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Blindness unilateral subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Diplopia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Eyelid oedema subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Lacrimation increased subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Photopsia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 0 |
| Vision blurred | | | |

| | | | |
|---|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Visual impairment subjects affected / exposed occurrences (all) | 8 / 17 (47.06%) 8 | 4 / 9 (44.44%) 4 | 5 / 18 (27.78%) 7 |
| Vitreous floaters subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Eye pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 18 (0.00%) 0 |
| Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Abdominal distension subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 5 / 17 (29.41%) 7 | 1 / 9 (11.11%) 3 | 2 / 18 (11.11%) 2 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 18 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 6 / 17 (35.29%) 9 | 0 / 9 (0.00%) 0 | 2 / 18 (11.11%) 3 |
| Abdominal tenderness subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 9 (11.11%) 0 | 0 / 18 (0.00%) 0 |
| Ascites subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |

| | | | |
|-----------------------------|------------------|----------------|-----------------|
| Constipation | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 1 / 9 (11.11%) | 3 / 18 (16.67%) |
| occurrences (all) | 7 | 1 | 3 |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 17 (64.71%) | 3 / 9 (33.33%) | 6 / 18 (33.33%) |
| occurrences (all) | 26 | 3 | 9 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Enteritis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 2 |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Hiatus hernia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 5 / 9 (55.56%) | 7 / 18 (38.89%) |
| occurrences (all) | 16 | 9 | 14 |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| | | | |
|--|------------------|----------------|-----------------|
| Proctitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Toothache | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 10 / 17 (58.82%) | 3 / 9 (33.33%) | 6 / 18 (33.33%) |
| occurrences (all) | 29 | 8 | 11 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 7 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Biliary dilatation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 3 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Acne | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Skin lesion | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hair disorder | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hair growth abnormal | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hand dermatitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hirsutism | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 2 | 0 | 1 |
| Onychomadesis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nail disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nail discolouration | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mechanical urticaria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 1 | 0 | 1 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Muscle disorder | | | |

| | | | |
|--------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Joint effusion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Costochondritis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Muscle fatigue | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pseudarthrosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 1 | 0 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 4 | 0 | 1 |
| Muscular weakness | | | |

| | | | |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Infections and infestations | | | |
| Klebsiella infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelid folliculitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Genital herpes | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 1 / 9 (11.11%) | 1 / 18 (5.56%) |
| occurrences (all) | 6 | 1 | 2 |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|-----------------------------------|-----------------|----------------|----------------|
| Oral herpes | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pelvic infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 9 (22.22%) | 1 / 18 (5.56%) |
| occurrences (all) | 4 | 3 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 1 / 9 (11.11%) | 0 / 18 (0.00%) |
| occurrences (all) | 15 | 14 | 0 |
| Vaginal infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 9 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 9 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|-----------------------|----------------------|----------------------|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 17 (35.29%) 17 | 1 / 9 (11.11%) 1 | 2 / 18 (11.11%) 4 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 17 (17.65%) 4 | 3 / 9 (33.33%) 3 | 4 / 18 (22.22%) 4 |
| Hypoproteinaemia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 18 (11.11%) 2 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 11 | 2 / 9 (22.22%) 8 | 1 / 18 (5.56%) 1 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 18 (11.11%) 2 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 9 (0.00%) 0 | 3 / 18 (16.67%) 4 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 4 | 1 / 9 (11.11%) 2 | 2 / 18 (11.11%) 3 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 3 / 9 (33.33%) 17 | 3 / 18 (16.67%) 6 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | 0 / 9 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 18 (0.00%) 0 |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 18 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 26 July 2010 | Additional safety monitoring language for pneumonitis; inclusion/exclusion criteria updated |
| 17 December 2010 | Removal of 150mg capsule strength; further clarification given on Dose Modifications for drug related toxicities; introduction of SAE reporting requirements for Drug Induced Liver Injury; inclusion/exclusion criteria updated. |
| 17 July 2012 | 1. Protocol summary: New safety language included; 2. Table 1. Schedule of Activities: New safety monitoring added (urinalysis), changes to study conduct (decrease in visit frequency, addition of bone marrow biopsy and/or aspirates for lymphoma patients); 3. Protocol sections 2 and 3: Changes the analysis tool for evaluating disease response in lymphoma patients and thus changes the conduct of the trial; 4. Protocol section 4: Conduct of study altered by shortened chemotherapy washout period and requirement for measurable disease at study entry. New safety language added to minimize risk of exposure in utero; 5. Protocol section 5: Specification of acceptable contraceptive measures constitutes change in study conduct, new safety language added; 6. Protocol section 7: Addition of PET and bone marrow biopsy constitute change in study conduct; 8. Protocol section 9: New efficacy descriptors constitute change in study conduct; 10. References and addition of new disease response criteria constitutes a change in study conduct was added in appendix 4. |
| 19 April 2013 | Non-substantia changes were made for updating the protocol with new text as required by the new protocol template. |
| 13 August 2015 | 1. Protocol summary: A reduced schedule of activities were updated, 2. Protocol section 4: new requirements about contraception and an updated definition of females of non-child-bearing potential have been added; 3. protocol section 5: Additional details about the requirements for drug storage condition, concomitant medications and patient management regarding bradycardia, change in the dosing guidance regarding pneumonitis, and additional guidance for renal cyst were added; 4. Protocol section 12: details on the assent and de identification procedures were added; 5. protocol section 15: clarifications to the Pfizer public disclosure procedure have been provided. 6. protocol section appendix 5: the schedule of activities has been reduced. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported