



Clinical trial results:

A Phase I, open-label, dose escalation study of ceritinib in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2012-002074-31 |
| Trial protocol | DE NL GB IT FR ES |
| Global end of trial date | 26 April 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 11 November 2019 |
| First version publication date | 11 November 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CLDK378X2103 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01742286 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com |

Notes:

Paediatric regulatory details

| | |
|---------------------------------------|----|
| Is trial part of an agreed paediatric | No |
|---------------------------------------|----|

| | |
|--|----|
| investigation plan (PIP) | |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Notes: | |

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 April 2019 |
| Is this the analysis of the primary completion data? | No |
| Notes: | |
| | |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 April 2019 |
| Was the trial ended prematurely? | No |
| Notes: | |

General information about the trial

Main objective of the trial:

Estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of ceritinib as a single agent when administered orally to pediatric patients with ALK-activated tumors in fasting and fed states.

Fasted cohort: each daily dose of LDK378 (including days which involved PK blood sampling) was taken at least 2 hours after last meal & subjects did not eat until 1 hour after LDK378 was taken. Each daily dose of LDK378 was taken with 1-2 tablespoons (15-30 mL) of an appropriate food (such as applesauce or non-fat yogurt) & a glass of water

Fed cohort: each daily dose of LDK378 (including days which involved PK blood sampling) was taken with, or within 30 minutes after finishing a low-fat light snack containing 100-300 calories & 1.5-2 grams of fat.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 12 February 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Australia: 6 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | France: 12 |
| Country: Number of subjects enrolled | Germany: 30 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Netherlands: 5 |
| Country: Number of subjects enrolled | Spain: 11 |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects | 83 |
| EEA total number of subjects | 67 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 5 |
| Children (2-11 years) | 48 |
| Adolescents (12-17 years) | 30 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Eighty-three subjects were treated at different dose levels in both fasted and fed states dose escalation and expansion groups. Forty subjects were treated with ceritinib in the dose escalation phase of the study. Twenty-five subjects were treated with ceritinib in fasted condition in dose escalation.

Pre-assignment

Screening details:

At least 15 subjects for the fasted dose escalation & 12 subjects for the fed dose escalation were expected to be treated. During the expansion part, approx. 45 subjects were planned to be treated on the preferred regimen, approx. 25 in group 1 (ALK-activated neuroblastoma) & approx. 20 in group 2 (other ALK-activated tumor such as IMT or ALCL).

Period 1

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

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Fasted: Ceritinib 300 mg/m2 |

Arm description:

Participants in the fasted group who took 300 mg of ceritinib

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ceritinib |
| Investigational medicinal product code | LDK378 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use, Nasogastric use , Gastric use |

Dosage and administration details:

300 mg/m2 Ceritinib was administered once daily by mouth, or by nasogastric tube or gastric tube.

| | |
|------------------|-----------------------------|
| Arm title | Fasted: Ceritinib 450 mg/m2 |
|------------------|-----------------------------|

Arm description:

Participants in the fasted group who took 450 mg of ceritinib

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ceritinib |
| Investigational medicinal product code | LDK378 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use, Nasogastric use , Gastric use |

Dosage and administration details:

450 mg/m2 Ceritinib was administered once daily by mouth, or by nasogastric tube or gastric tube.

| | |
|------------------|-----------------------------|
| Arm title | Fasted: Ceritinib 510 mg/m2 |
|------------------|-----------------------------|

Arm description:

Participants in the fasted group who took 510 mg of ceritinib

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|---|
| Investigational medicinal product name | Ceritinib |
| Investigational medicinal product code | LDK378 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use, Nasogastric use , Gastric use |
| Dosage and administration details: | |
| 510 mg/m2 Ceritinib was administered once daily by mouth, or by nasogastric tube or gastric tube. | |
| Arm title | Fasted: Ceritinib 560 mg/m2 |
| Arm description: | |
| Participants in the fasted group who took 560 mg of ceritinib | |
| Arm type | Experimental |
| Investigational medicinal product name | Ceritinib |
| Investigational medicinal product code | LDK378 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use, Nasogastric use , Gastric use |
| Dosage and administration details: | |
| 560 mg/m2 Ceritinib was administered once daily by mouth, or by nasogastric tube or gastric tube. | |
| Arm title | Fed: Ceritinib 320 mg/m2 |
| Arm description: | |
| Participants in the fed group who took 320 mg of ceritinib | |
| Arm type | Experimental |
| Investigational medicinal product name | Ceritinib |
| Investigational medicinal product code | LDK378 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use, Nasogastric use , Gastric use |
| Dosage and administration details: | |
| 320 mg/m2 Ceritinib was administered once daily by mouth, or by nasogastric tube or gastric tube. | |
| Arm title | Fed: Ceritinib 400 mg/m2 |
| Arm description: | |
| Participants in the fed group who took 400 mg of ceritinib | |
| Arm type | Experimental |
| Investigational medicinal product name | Ceritinib |
| Investigational medicinal product code | LDK378 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use, Nasogastric use , Gastric use |
| Dosage and administration details: | |
| 400 mg/m2 Ceritinib was administered once daily by mouth, or by nasogastric tube or gastric tube. | |
| Arm title | Fed: Ceritinib 500 mg/m2 |
| Arm description: | |
| Participants in the fed group who took 500 mg of ceritinib | |
| Arm type | Experimental |
| Investigational medicinal product name | Ceritinib |
| Investigational medicinal product code | LDK378 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use, Nasogastric use , Gastric use |

Dosage and administration details:

500 mg/m² Ceritinib was administered once daily by mouth, or by nasogastric tube or gastric tube.

| Number of subjects in period 1 | Fasted: Ceritinib 300 mg/m ² | Fasted: Ceritinib 450 mg/m ² | Fasted: Ceritinib 510 mg/m ² |
|---------------------------------------|--|--|--|
| Started | 5 | 12 | 13 |
| Ended Treatment = Not Completed) | 5 | 12 | 13 |
| Completed | 0 | 0 | 0 |
| Not completed | 5 | 12 | 13 |
| Adverse event, serious fatal | - | - | - |
| Physician decision | - | 3 | 4 |
| Consent withdrawn by subject | - | - | - |
| Disease progression | 3 | 7 | 7 |
| Adverse event, non-fatal | - | 1 | 2 |
| Administrative problems | 1 | 1 | - |
| Patient/guardian decision | 1 | - | - |

| Number of subjects in period 1 | Fasted: Ceritinib 560 mg/m ² | Fed: Ceritinib 320 mg/m ² | Fed: Ceritinib 400 mg/m ² |
|---------------------------------------|--|---|---|
| Started | 2 | 4 | 5 |
| Ended Treatment = Not Completed) | 2 | 4 | 5 |
| Completed | 0 | 0 | 0 |
| Not completed | 2 | 4 | 5 |
| Adverse event, serious fatal | - | - | 1 |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject | - | - | - |
| Disease progression | 1 | 4 | 3 |
| Adverse event, non-fatal | - | - | 1 |
| Administrative problems | - | - | - |
| Patient/guardian decision | - | - | - |

| Number of subjects in period 1 | Fed: Ceritinib 500 mg/m ² |
|---------------------------------------|---|
| Started | 42 |
| Ended Treatment = Not Completed) | 42 |
| Completed | 0 |
| Not completed | 42 |
| Adverse event, serious fatal | - |
| Physician decision | 11 |

| | |
|------------------------------|----|
| Consent withdrawn by subject | 1 |
| Disease progression | 17 |
| Adverse event, non-fatal | 6 |
| Administrative problems | 7 |
| Patient/guardian decision | - |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------------|
| Reporting group title | Fasted: Ceritinib 300 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 300 mg of ceritinib | |
| Reporting group title | Fasted: Ceritinib 450 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 450 mg of ceritinib | |
| Reporting group title | Fasted: Ceritinib 510 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 510 mg of ceritinib | |
| Reporting group title | Fasted: Ceritinib 560 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 560 mg of ceritinib | |
| Reporting group title | Fed: Ceritinib 320 mg/m2 |
| Reporting group description: | |
| Participants in the fed group who took 320 mg of ceritinib | |
| Reporting group title | Fed: Ceritinib 400 mg/m2 |
| Reporting group description: | |
| Participants in the fed group who took 400 mg of ceritinib | |
| Reporting group title | Fed: Ceritinib 500 mg/m2 |
| Reporting group description: | |
| Participants in the fed group who took 500 mg of ceritinib | |

| Reporting group values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 |
|----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Number of subjects | 5 | 12 | 13 |
| Age, Customized | | | |
| Units: Subjects | | | |
| 1 - < 7 yrs | 1 | 4 | 6 |
| 7 - < 12 yrs | 2 | 2 | 1 |
| 12 - < 18 yrs | 2 | 6 | 6 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 11.6 | 10.0 | 9.2 |
| standard deviation | ± 5.27 | ± 4.94 | ± 5.34 |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | 5 |
| Male | 2 | 9 | 8 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian | 0 | 1 | 1 |
| Black | 0 | 1 | 0 |
| Caucasian | 5 | 7 | 11 |
| Other | 0 | 3 | 1 |
| Native American | 0 | 0 | 0 |

| Reporting group values | Fasted: Ceritinib 560 mg/m2 | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 |
|---|--------------------------------|-----------------------------|-----------------------------|
| Number of subjects | 2 | 4 | 5 |
| Age, Customized Units: Subjects | | | |
| 1 - < 7 yrs | 1 | 2 | 2 |
| 7 - < 12 yrs | 0 | 0 | 1 |
| 12 - < 18 yrs | 1 | 2 | 2 |
| Age Continuous Units: years | | | |
| arithmetic mean | 9.0 | 8.8 | 9.2 |
| standard deviation | ± 9.90 | ± 4.99 | ± 4.02 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 1 | 1 | 3 |
| Male | 1 | 3 | 2 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 0 | 0 | 0 |
| Black | 0 | 0 | 0 |
| Caucasian | 2 | 4 | 3 |
| Other | 0 | 0 | 2 |
| Native American | 0 | 0 | 0 |

| Reporting group values | Fed: Ceritinib 500 mg/m2 | Total | |
|---|-----------------------------|-------|--|
| Number of subjects | 42 | 83 | |
| Age, Customized Units: Subjects | | | |
| 1 - < 7 yrs | 21 | 37 | |
| 7 - < 12 yrs | 10 | 16 | |
| 12 - < 18 yrs | 11 | 30 | |
| Age Continuous Units: years | | | |
| arithmetic mean | 7.3 | | |
| standard deviation | ± 4.73 | - | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 14 | 30 | |
| Male | 28 | 53 | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 3 | 5 | |
| Black | 0 | 1 | |
| Caucasian | 33 | 65 | |
| Other | 5 | 11 | |
| Native American | 1 | 1 | |

Subject analysis sets

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | ALK-activated Neuroblastoma |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated neuroblastoma enrolled in the expansion part of the study and were given ceritinib once daily, continuously

| | |
|----------------------------|---|
| Subject analysis set title | ALK-activated Inflammatory myofibroblastic tumors (IMT) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated IMT enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| | |
|----------------------------|---|
| Subject analysis set title | ALK-activated Anaplastic large cell lymphoma (ALCL) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated ALCL enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| | |
|----------------------------|---------------------|
| Subject analysis set title | ALK-activated Other |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with other ALK-activated tumors enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | ALK-activated Neuroblastoma |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated neuroblastoma enrolled in the expansion part of the study and were given ceritinib once daily, continuously

| | |
|----------------------------|---|
| Subject analysis set title | ALK-activated Inflammatory myofibroblastic tumors (IMT) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated IMT enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| | |
|----------------------------|---|
| Subject analysis set title | ALK-activated Anaplastic large cell lymphoma (ALCL) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated ALCL enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| | |
|----------------------------|---------------------|
| Subject analysis set title | ALK-activated Other |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with other ALK-activated tumors enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| Reporting group values | ALK-activated Neuroblastoma | ALK-activated Inflammatory myofibroblastic tumors (IMT) | ALK-activated Anaplastic large cell lymphoma (ALCL) |
|------------------------------------|-----------------------------|---|---|
| Number of subjects | 30 | 10 | 8 |
| Age, Customized Units: Subjects | | | |
| 1 - < 7 yrs | | | |
| 7 - < 12 yrs | | | |
| 12 - < 18 yrs | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 20.0 | 70.0 | 75.0 |
| standard deviation | ± | ± | ± |

| | | | |
|---|--|--|--|
| Sex: Female, Male Units: Subjects | | | |
| Female Male | | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian Black Caucasian Other Native American | | | |

| Reporting group values | ALK-activated Other | ALK-activated Neuroblastoma | ALK-activated Inflammatory myofibroblastic tumors (IMT) |
|---|---------------------|-----------------------------|---|
| Number of subjects | 7 | 6 | 7 |
| Age, Customized Units: Subjects | | | |
| 1 - < 7 yrs 7 - < 12 yrs 12 - < 18 yrs | | | |
| Age Continuous Units: years arithmetic mean standard deviation | 14.3 ± | 15.0 ± | 99.99 ± |
| Sex: Female, Male Units: Subjects | | | |
| Female Male | | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian Black Caucasian Other Native American | | | |

| Reporting group values | ALK-activated Anaplastic large cell lymphoma (ALCL) | ALK-activated Other | |
|---|---|---------------------|--|
| Number of subjects | 6 | 1 | |
| Age, Customized Units: Subjects | | | |
| 1 - < 7 yrs 7 - < 12 yrs 12 - < 18 yrs | | | |
| Age Continuous Units: years arithmetic mean standard deviation | 99.99 ± | 99.99 ± | |

| | | | |
|---|--|--|--|
| Sex: Female, Male Units: Subjects | | | |
| Female Male | | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian Black Caucasian Other Native American | | | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Fasted: Ceritinib 300 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 300 mg of ceritinib | |
| Reporting group title | Fasted: Ceritinib 450 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 450 mg of ceritinib | |
| Reporting group title | Fasted: Ceritinib 510 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 510 mg of ceritinib | |
| Reporting group title | Fasted: Ceritinib 560 mg/m2 |
| Reporting group description: | |
| Participants in the fasted group who took 560 mg of ceritinib | |
| Reporting group title | Fed: Ceritinib 320 mg/m2 |
| Reporting group description: | |
| Participants in the fed group who took 320 mg of ceritinib | |
| Reporting group title | Fed: Ceritinib 400 mg/m2 |
| Reporting group description: | |
| Participants in the fed group who took 400 mg of ceritinib | |
| Reporting group title | Fed: Ceritinib 500 mg/m2 |
| Reporting group description: | |
| Participants in the fed group who took 500 mg of ceritinib | |
| Subject analysis set title | ALK-activated Neuroblastoma |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants with ALK-activated neuroblastoma enrolled in the expansion part of the study and were given ceritinib once daily, continuously | |
| Subject analysis set title | ALK-activated Inflammatory myofibroblastic tumors (IMT) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants with ALK-activated IMT enrolled in the expansion part of the study who were given ceritinib once daily, continuously | |
| Subject analysis set title | ALK-activated Anaplastic large cell lymphoma (ALCL) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants with ALK-activated ALCL enrolled in the expansion part of the study who were given ceritinib once daily, continuously | |
| Subject analysis set title | ALK-activated Other |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants with other ALK-activated tumors enrolled in the expansion part of the study who were given ceritinib once daily, continuously | |
| Subject analysis set title | ALK-activated Neuroblastoma |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants with ALK-activated neuroblastoma enrolled in the expansion part of the study and were given ceritinib once daily, continuously | |
| Subject analysis set title | ALK-activated Inflammatory myofibroblastic tumors (IMT) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated IMT enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| | |
|----------------------------|---|
| Subject analysis set title | ALK-activated Anaplastic large cell lymphoma (ALCL) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with ALK-activated ALCL enrolled in the expansion part of the study who were given ceritinib once daily, continuously

| | |
|----------------------------|---------------------|
| Subject analysis set title | ALK-activated Other |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with other ALK-activated tumors enrolled in the expansion part of the study who were given ceritinib once daily, continuously

Primary: Incidence rate of Dose Limiting Toxicities (DLTs) occurring during first cycle of treatment

| | |
|-----------------|--|
| End point title | Incidence rate of Dose Limiting Toxicities (DLTs) occurring during first cycle of treatment ^[1] |
|-----------------|--|

End point description:

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant therapies that occurs within the first 21 days of treatment with LDK378 and meets a specified defined criteria. A participant with multiple occurrences of DLTs under one treatment is counted only once in the Adverse Event category for that treatment. A participant with multiple DLTs within a primary system organ class is counted only once in the total row.

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

End point timeframe:

up to day 21 after the patient's first dose; cycle = within the first 21 days of patient's first dose

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 for this endpoint

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 12 | 6 | 2 |
| Units: Participants | | | | |
| Investigations: Alanine aminotransferase incr. | 0 | 0 | 0 | 1 |
| Gastrointestinal disorders: abdominal pain | 0 | 0 | 0 | 1 |
| Gastrointestinal disorders: Influenza | 0 | 0 | 0 | 0 |
| Total DLTs | 0 | 0 | 0 | 2 |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|--|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 4 | 5 | |
| Units: Participants | | | | |
| Investigations: Alanine aminotransferase incr. | 0 | 1 | 0 | |
| Gastrointestinal disorders: abdominal pain | 0 | 0 | 0 | |

| | | | | |
|---------------------------------------|---|---|---|--|
| Gastrointestinal disorders: Influenza | 0 | 0 | 1 | |
| Total DLTs | 0 | 1 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of best overall response by Overall response Rate (ORR) per Investigator assessment

| | |
|---|---|
| End point title | Summary of best overall response by Overall response Rate (ORR) per Investigator assessment |
| End point description: Assessed the anti-tumor activity of LDK378 per investigator assessment of disease status using RECIST 1.1 by treatment group. | |
| End point type | Secondary |
| End point timeframe: 30 months | |

| End point values | ALK-activated Neuroblastoma | ALK-activated Inflammatory myofibroblastic tumors (IMT) | ALK-activated Anaplastic large cell lymphoma (ALCL) | ALK-activated Other |
|-----------------------------------|-----------------------------|---|---|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 10 | 8 | 7 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 20.0 (7.7 to 38.6) | 70.0 (34.8 to 93.3) | 75.0 (34.9 to 96.8) | 14.3 (0.4 to 57.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) per investigator assessment

| | |
|--|--|
| End point title | Duration of response (DoR) per investigator assessment |
| End point description: Assess the anti-tumor activity of LDK378 per DOR by primary diagnosis of tumor | |
| End point type | Secondary |
| End point timeframe: 30 months | |

| End point values | ALK-activated Neuroblastoma | ALK-activated Inflammatory myofibroblastic tumors (IMT) | ALK-activated Anaplastic large cell lymphoma (ALCL) | ALK-activated Other |
|----------------------------------|-----------------------------|---|---|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 7 | 6 | 1 |
| Units: months | | | | |
| median (confidence interval 95%) | 15.0 (5.8 to 22.2) | 999 (3.5 to 999) | 999 (2.8 to 999) | 999 (999 to 999) |

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: Assess the anti-tumor activity of LDK378 as per RECIST 1.1 by PFS by primary diagnosis of tumor | |
| End point type | Secondary |
| End point timeframe: 30 months | |

| End point values | ALK-activated Neuroblastoma | ALK-activated Inflammatory myofibroblastic tumors (IMT) | ALK-activated Anaplastic large cell lymphoma (ALCL) | ALK-activated Other |
|----------------------------------|-----------------------------|---|---|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 10 | 6 | 1 |
| Units: months | | | | |
| median (confidence interval 95%) | 2.4 (1.2 to 6.8) | 999 (1.2 to 999) | 999 (4.1 to 999) | 1.9 (1.2 to 999) |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration time profiles by treatment group in escalation phase

| | |
|---|---|
| End point title | Plasma concentration time profiles by treatment group in escalation phase |
| End point description: Characterize single and multiple-dose PK of LDK378 in pediatric patients. Only PK plasma concentrations with non-missing sampling date and time, and for which the last dose date and time prior to the PK sample draw are non-missing, were included in the PK analysis. | |
| End point type | Secondary |

End point timeframe:

0hr pre-dose, 2hrs post-dose, 4hrs post-dose, 6hrs post-dose & 24hrs post-dose in Cycle1 Day1 & Cycle 2 day 1; 0hr pre-dose in Cycle 1 Day 15, Cycle 2 Day1, Cycle 2 Day 2, Cycle 3 day 1 & Cycle 4 Day 1

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|---|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 13 | 2 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle1 Day1 (C1D1) 0 hr pre-dose(n=5,12,6,2,4,5,5) | 0.0 (± 0.0) | 0.0 (± 0.0) | 0.0 (± 0.0) | 0.0 (± 0.0) |
| C1D1 2 hrs post-dose(n=5,11,6,2,4,5,5) | 104 (± 97.9) | 99.0 (± 94.7) | 112 (± 90.6) | 126 (± 0.6) |
| C1D1 4 hrs post-dose(n=5,11,6,2,4,5,5) | 216 (± 39.6) | 233 (± 69.0) | 250 (± 93.5) | 350 (± 54.7) |
| C1D1 6 hrs post-dose(n=5,11,6,2,4,5,4) | 227 (± 33.8) | 245 (± 78.1) | 245 (± 97.2) | 423 (± 74.2) |
| C1D1 24 hrs post-dose(n=5,11,6,2,4,5,4) | 130 (± 66.3) | 141 (± 89.9) | 86.4 (± 117.2) | 268 (± 73.6) |
| C1D2 0 hr pre-dose(n=5,11,6,2,4,5,4) | 130 (± 66.3) | 141 (± 89.9) | 86.4 (± 117.2) | 268 (± 73.6) |
| C1D15 0 hr pre-dose(n=5,12,6,2,3,4,5) | 193 (± 99.6) | 618 (± 64.6) | 537 (± 49.9) | 942 (± 5.1) |
| C2D1 0 hr pre-dose(n=5,12,5,2,3,4,3) | 169 (± 299.5) | 661 (± 53.5) | 672 (± 45.4) | 695 (± 152.7) |
| C2D1 2 hrs post-dose(n=5,12,5,2,3,4,3) | 287 (± 85.4) | 687 (± 61.6) | 801 (± 45.9) | 662 (± 99.6) |
| C2D1 4 hrs post-dose(n=5,12,5,2,3,4,3) | 386 (± 47.6) | 810 (± 51.9) | 1000 (± 30.4) | 1230 (± 30.1) |
| C2D1 6 hrs post-dose(n=5,12,5,2,3,4,2) | 426 (± 38.4) | 852 (± 47.8) | 898 (± 37.6) | 1260 (± 16.4) |
| C2D1 24 hrs post-dose(n=5,12,5,2,3,4,5) | 247 (± 46.9) | 651 (± 53.7) | 714 (± 40.8) | 847 (± 72.2) |
| C2D2 0 hr pre-dose(n=5,12,5,2,3,4,5) | 247 (± 46.9) | 651 (± 53.7) | 714 (± 40.8) | 847 (± 72.2) |
| C3D1 0 hr pre-dose(n=2,8,4,1,2,1,5) | 399 (± 94.4) | 810 (± 34.3) | 415 (± 117.7) | 1320 (± 0.0) |
| C4D1 0 hr pre-dose(n=2,8,4,1,1,1,3) | 503 (± 35.1) | 960 (± 36.2) | 321 (± 874.8) | 857 (± 0.0) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|---|-----------------------------|-----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 21 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle1 Day1 (C1D1) 0 hr pre-dose(n=5,12,6,2,4,5,5) | 0.0 (± 0.0) | 0.0 (± 0.0) | 0.0 (± 0.0) | |
| C1D1 2 hrs post-dose(n=5,11,6,2,4,5,5) | 52.4 (± 138.1) | 197 (± 58.3) | 72.5 (± 82.3) | |
| C1D1 4 hrs post-dose(n=5,11,6,2,4,5,5) | 166 (± 92.8) | 311 (± 28.1) | 153 (± 34.1) | |
| C1D1 6 hrs post-dose(n=5,11,6,2,4,5,4) | 275 (± 35.3) | 318 (± 36.7) | 168 (± 68.9) | |

| | | | | |
|---|---------------|---------------|---------------|--|
| C1D1 24 hrs post-dose(n=5,11,6,2,4,5,4) | 98.5 (± 63.7) | 126 (± 107.7) | 161 (± 111.3) | |
| C1D2 0 hr pre-dose(n=5,11,6,2,4,5,4) | 98.5 (± 63.7) | 126 (± 107.7) | 161 (± 111.3) | |
| C1D15 0 hr pre-dose(n=5,12,6,2,3,4,5) | 262 (± 118.4) | 379 (± 119.2) | 461 (± 76.3) | |
| C2D1 0 hr pre-dose(n=5,12,5,2,3,4,3) | 218 (± 103.7) | 429 (± 73.8) | 655 (± 12.4) | |
| C2D1 2 hrs post-dose(n=5,12,5,2,3,4,3) | 196 (± 112.4) | 475 (± 96.6) | 718 (± 21.1) | |
| C2D1 4 hrs post-dose(n=5,12,5,2,3,4,3) | 262 (± 133.9) | 631 (± 86.6) | 744 (± 13.2) | |
| C2D1 6 hrs post-dose(n=5,12,5,2,3,4,2) | 300 (± 130.3) | 648 (± 105.5) | 786 (± 7.7) | |
| C2D1 24 hrs post-dose(n=5,12,5,2,3,4,5) | 194 (± 106.5) | 411 (± 147.3) | 448 (± 43.9) | |
| C2D2 0 hr pre-dose(n=5,12,5,2,3,4,5) | 194 (± 106.5) | 411 (± 147.3) | 448 (± 43.9) | |
| C3D1 0 hr pre-dose(n=2,8,4,1,2,1,5) | 167 (± 218.3) | 328 (± 0.0) | 433 (± 128.5) | |
| C4D1 0 hr pre-dose(n=2,8,4,1,1,1,3) | 403 (± 0.0) | 1320 (± 0.0) | 658 (± 27.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration time profiles by treatment group in expansion phase

| | |
|---|--|
| End point title | Plasma concentration time profiles by treatment group in expansion phase |
| End point description: | |
| Characterize single and multiple-dose PK of LDK378 in pediatric patients. Only PK plasma concentrations with non-missing sampling date and time, and for which the last dose date and time prior to the PK sample draw are non-missing, were included in the PK analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| 0hr pre-dose Cycle 1 Day 1, cycle 1 Day 15; 0hr pre-dose, 2hrs post-dose, 4hrs post-dose, 6hrs post-dose & 24hrs post-dose in Cycle2 Day1; 0hr pre-dose in Cycle2 Day2, Cycle 3 Day 1 & Cycle 4 Day 1 | |

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|---|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 13 | 2 |
| Units: mg/mg^2 | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| C1D1 0 hr pre-dose(n=0,0,6,0,0,0,9) | 999 (± 999) | 999 (± 999) | 0.0 (± 0.0) | 999 (± 999) |
| C1D15 0 hr post-dose(n=0,0,1,0,0,0,0) | 999 (± 999) | 999 (± 999) | 1190 (± 0.0) | 999 (± 999) |
| C2D1 0 hr pre-dose(n=0,0,7,0,0,0,16) | 999 (± 999) | 999 (± 999) | 529 (± 365.4) | 999 (± 999) |
| C2D1 2 hrs post-dose(n=0,0,7,0,0,0,15) | 999 (± 999) | 999 (± 999) | 798 (± 69.0) | 999 (± 999) |
| C2D1 4 hrs post-dose(n=0,0,7,0,0,0,4) | 999 (± 999) | 999 (± 999) | 863 (± 65.2) | 999 (± 999) |
| C2D1 6 hrs post-dose(n=0,0,7,0,0,0,15) | 999 (± 999) | 999 (± 999) | 939 (± 71.4) | 999 (± 999) |

| | | | | |
|---|-------------|-------------|---------------|-------------|
| C2D1 24 hrs post-dose(n=0,0,6,0,0,0,14) | 999 (± 999) | 999 (± 999) | 615 (± 119.9) | 999 (± 999) |
| C2D2 0 hr pre-dose(n=0,0,6,0,0,0,14) | 999 (± 999) | 999 (± 999) | 615 (± 119.9) | 999 (± 999) |
| C3D1 0 hr pre-dose(n=0,0,5,0,0,0,14) | 999 (± 999) | 999 (± 999) | 836 (± 60.4) | 999 (± 999) |
| C4D1 0 hr pre-dose(n=0,0,5,0,0,0,12) | 999 (± 999) | 999 (± 999) | 834 (± 78.8) | 999 (± 999) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|---|-----------------------------|-----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 21 | |
| Units: mg/mg^2 | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| C1D1 0 hr pre-dose(n=0,0,6,0,0,0,9) | 999 (± 999) | 999 (± 999) | 0.0 (± 0.0) | |
| C1D15 0 hr post-dose(n=0,0,1,0,0,0,0) | 999 (± 999) | 999 (± 999) | 999 (± 999) | |
| C2D1 0 hr pre-dose(n=0,0,7,0,0,0,16) | 999 (± 999) | 999 (± 999) | 627 (± 93.6) | |
| C2D1 2 hrs post-dose(n=0,0,7,0,0,0,15) | 999 (± 999) | 999 (± 999) | 729 (± 72.3) | |
| C2D1 4 hrs post-dose(n=0,0,7,0,0,0,4) | 999 (± 999) | 999 (± 999) | 828 (± 47.9) | |
| C2D1 6 hrs post-dose(n=0,0,7,0,0,0,15) | 999 (± 999) | 999 (± 999) | 870 (± 52.6) | |
| C2D1 24 hrs post-dose(n=0,0,6,0,0,0,14) | 999 (± 999) | 999 (± 999) | 596 (± 75.5) | |
| C2D2 0 hr pre-dose(n=0,0,6,0,0,0,14) | 999 (± 999) | 999 (± 999) | 596 (± 75.5) | |
| C3D1 0 hr pre-dose(n=0,0,5,0,0,0,14) | 999 (± 999) | 999 (± 999) | 573 (± 134.2) | |
| C4D1 0 hr pre-dose(n=0,0,5,0,0,0,12) | 999 (± 999) | 999 (± 999) | 622 (± 96.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameters: AUC0 - 24h & AUClast in Cycle 1 Day 1 - Dose escalation phase (single dose)

| | |
|-----------------|---|
| End point title | Pharmacokinetics (PK) parameters: AUC0 - 24h & AUClast in Cycle 1 Day 1 - Dose escalation phase (single dose) |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. AUC: Area under the plasma (serum, or blood) concentration versus time curve AUClast: Area under the plasma (serum, or blood) concentration versus time curve under the concentration-time curve from time zero to the last measureable concentration time AUC0-24h: AUC0-24h Area under the plasma concentration-time curve t=0-24 h

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|---|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 10 | 2 |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC0-24h (n=4,3,2,0,1,1,2) | 3920 (± 39.9) | 5220 (± 58.0) | 8750 (± 11.1) | 999 (± 999) |
| AUClast (n= 5,9,3,1,3,4,3) | 4260 (± 39.3) | 4350 (± 91.8) | 7670 (± 24.5) | 4860 (± 0.0) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|---|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 4 | 18 | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC0-24h (n=4,3,2,0,1,1,2) | 5720 (± 0.0) | 7272 (± 0.0) | 4730 (± 59.4) | |
| AUClast (n= 5,9,3,1,3,4,3) | 3730 (± 48.6) | 5760 (± 49.1) | 4940 (± 32.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameters: AUC0 - 24h & AUClast in Cycle 2 Day 1 - Dose escalation phase (single dose)

| | |
|-----------------|---|
| End point title | Pharmacokinetics (PK) parameters: AUC0 - 24h & AUClast in Cycle 2 Day 1 - Dose escalation phase (single dose) |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. AUC: Area under the plasma (serum, or blood) concentration versus time curve AUClast: Area under the plasma (serum, or blood) concentration versus time curve under the concentration-time curve from time zero to the last measureable concentration time AUC0-24h: AUC0-24h Area under the plasma concentration-time curve t=0-24 h

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|---|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 10 | 2 |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC0-24h (n=5,7,2,2,1,1,1) | 8160 (± 44.0) | 16900 (± 59.1) | 21000 (± 20.8) | 25300 (± 39.2) |

| | | | | |
|-----------------------------|---------------|----------------|----------------|----------------|
| AUClast (n= 5,12,5,2,3,4,2) | 8210 (± 44.3) | 18000 (± 50.0) | 17200 (± 51.2) | 25600 (± 39.0) |
|-----------------------------|---------------|----------------|----------------|----------------|

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|---|-----------------------------|-----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 4 | 18 | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC0-24h (n=5,7,2,2,1,1,1) | 2100 (± 0.0) | 30500 (± 0.0) | 16500 (± 0.0) | |
| AUClast (n= 5,12,5,2,3,4,2) | 5840 (± 118.4) | 125000 (± 113.2) | 16700 (± 1.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameters: AUC0 - 24h & AUClast in Cycle 2 Day 1 - Dose expansion phase (multiple dose)

| | |
|-----------------|---|
| End point title | Pharmacokinetics (PK) parameters: AUC0 - 24h & AUClast in Cycle 2 Day 1 - Dose expansion phase (multiple dose) ^[2] |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. In this phase ceritinib was expanded at 500mg/m2 fed and 510mg/m2 fasted administered orally once daily and was assessed only at steady state, Cycle 2 Day 1. AUC: Area under the plasma (serum, or blood) concentration versus time curve AUClast: Area under the plasma (serum, or blood) concentration versus time curve area under the concentration-time curve from time zero to the last measureable concentration time AUC0-24h: AUC0-24h Area under the plasma concentration-time curve t=0-24 h

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

| End point values | Fasted: Ceritinib 510 mg/m2 | Fed: Ceritinib 500 mg/m2 | | |
|---|-----------------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 18 | | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC0-24h (n = 0, 6) | 999 (± 999) | 15900 (± 93.8) | | |
| AUClast (n = 4, 14) | 24100 (± 38.9) | 16100 (± 61.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Cmax in Cycle 1 Day 1 - Dose escalation phase (single dose)

| | |
|-----------------|---|
| End point title | PK parameter: Cmax in Cycle 1 Day 1 - Dose escalation phase (single dose) |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. Cmax: Maximum (peak) concentration of drug

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|---|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 10 | 2 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 258 (± 39.0) | 270 (± 82.1) | 537 (± 22.2) | 265 (± 0.0) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|---|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 4 | 18 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 251 (± 37.0) | 341 (± 34.2) | 204 (± 54.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Cmax in Cycle 2 Day 1 - Dose escalation phase (single dose)

| | |
|-----------------|---|
| End point title | PK parameter: Cmax in Cycle 2 Day 1 - Dose escalation phase (single dose) |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. Cmax: Maximum (peak) concentration of drug.

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|---|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 10 | 2 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 427 (± 38.5) | 870 (± 48.7) | 1020 (± 32.1) | 1300 (± 21.4) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|---|-----------------------------|-----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 4 | 18 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 300 (± 130.3) | 674 (± 93.8) | 804 (± 10.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Cmax in Cycle 2 Day 1 - Dose expansion phase (multiple dose)

| | |
|-----------------|---|
| End point title | PK parameter: Cmax in Cycle 2 Day 1 - Dose expansion phase (multiple dose) ^[3] |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. In this phase ceritinib was expanded at 500mg/m2 fed and 510mg/m2 fasted administered orally once daily and was assessed only at steady state, Cycle 2 Day 1. Cmax: Maximum (peak) concentration of drug

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

| End point values | Fasted: Ceritinib 510 mg/m2 | Fed: Ceritinib 500 mg/m2 | | |
|---|-----------------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 18 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1220 (± 40.2) | 890 (± 50.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Tmax in Cycle 1 Day 1 - Dose escalation phase (single dose)

| | |
|-----------------|---|
| End point title | PK parameter: Tmax in Cycle 1 Day 1 - Dose escalation phase (single dose) |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. Tmax: The time to reach maximum plasma concentration

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|-------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 10 | 2 |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 4.20 (1.90 to 24.0) | 4.25 (0.00 to 6.10) | 4.30 (4.10 to 6.00) | 6.10 (6.10 to 6.10) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|-------------------------------|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 4 | 18 | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 6.10 (5.70 to 6.30) | 6.00 (4.30 to 6.20) | 5.80 (4.10 to 6.10) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Tmax in Cycle 2 Day 1 - Dose escalation phase (single dose)

| | |
|-----------------|---|
| End point title | PK parameter: Tmax in Cycle 2 Day 1 - Dose escalation phase (single dose) |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. Tmax: The time to reach maximum plasma concentration

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|-------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 10 | 2 |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 6.00 (4.10 to 6.70) | 5.10 (2.00 to 6.60) | 4.00 (2.10 to 6.00) | 3.95 (0.00 to 6.70) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|-------------------------------|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 4 | 18 | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 5.90 (5.80 to 6.10) | 6.00 (4.00 to 6.10) | 2.20 (2.00 to 2.40) | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Tmax in Cycle 2 Day 1 - Dose expansion phase (multiple dose)

| | |
|-----------------|---|
| End point title | PK parameter: Tmax in Cycle 2 Day 1 - Dose expansion phase (multiple dose) ^[4] |
|-----------------|---|

End point description:

Characterize single and multiple-dose PK of LDK378 in pediatric patients. In this phase ceritinib was expanded at 500mg/m2 fed and 510mg/m2 fasted administered orally once daily and was assessed only at steady state, Cycle 2 Day 1. Characterize single and multiple-dose PK of LDK378 in pediatric patients. Tmax: The time to reach maximum plasma concentration

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

End point timeframe:

0hr pre-dose, 2, 4, 6 & 24hrs post-dose

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis was planned for this endpoint

| End point values | Fasted: Ceritinib 510 mg/m2 | Fed: Ceritinib 500 mg/m2 | | |
|-------------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 18 | | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 6.20 (3.80 to 23.8) | 5.90 (1.90 to 23.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Racc in Dose escalation phase Cycle 2 Day 1

| | |
|--|---|
| End point title | PK parameter: Racc in Dose escalation phase Cycle 2 Day 1 |
| End point description: | |
| Characterize single and multiple-dose PK of LDK378 in pediatric patients. Racc: Accumulation ratio | |
| End point type | Secondary |
| End point timeframe: | |
| 0hr pre-dose, 2, 4, 6 & 24hrs post-dose | |

| End point values | Fasted: Ceritinib 300 mg/m2 | Fasted: Ceritinib 450 mg/m2 | Fasted: Ceritinib 510 mg/m2 | Fasted: Ceritinib 560 mg/m2 |
|---|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 12 | 10 | 2 |
| Units: ratio | | | | |
| geometric mean (geometric coefficient of variation) | 41.6 (± 80.7) | 30.3 (± 116.3) | 22.8 (± 71.6) | 15.5 (± 0.0) |

| End point values | Fed: Ceritinib 320 mg/m2 | Fed: Ceritinib 400 mg/m2 | Fed: Ceritinib 500 mg/m2 | |
|---|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 4 | 18 | |
| Units: ratio | | | | |
| geometric mean (geometric coefficient of variation) | 95.0 (± 0.0) | 9.83 (± 0.0) | 19.3 (± 118.4) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 63.7 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Ceritinib@300 mg/m2 |
|-----------------------|---------------------|

Reporting group description:

Ceritinib@300 mg/m2

| | |
|-----------------------|---------------------|
| Reporting group title | Ceritinib@450 mg/m2 |
|-----------------------|---------------------|

Reporting group description:

Ceritinib@450 mg/m2

| | |
|-----------------------|---------------------|
| Reporting group title | Ceritinib@510 mg/m2 |
|-----------------------|---------------------|

Reporting group description:

Ceritinib@510 mg/m2

| | |
|-----------------------|---------------------|
| Reporting group title | Ceritinib@560 mg/m2 |
|-----------------------|---------------------|

Reporting group description:

Ceritinib@560 mg/m2

| | |
|-----------------------|---------------------|
| Reporting group title | Ceritinib@320 mg/m2 |
|-----------------------|---------------------|

Reporting group description:

Ceritinib@320 mg/m2

| | |
|-----------------------|---------------------|
| Reporting group title | Ceritinib@400 mg/m2 |
|-----------------------|---------------------|

Reporting group description:

Ceritinib@400 mg/m2

| | |
|-----------------------|---------------------|
| Reporting group title | Ceritinib@500 mg/m2 |
|-----------------------|---------------------|

Reporting group description:

Ceritinib@500 mg/m2

| | |
|-----------------------|-------------------------|
| Reporting group title | Fasted+Fed All Subjects |
|-----------------------|-------------------------|

Reporting group description:

All participants in the Fasted and Fed groups

| Serious adverse events | Ceritinib@300 mg/m2 | Ceritinib@450 mg/m2 | Ceritinib@510 mg/m2 |
|---|---------------------|---------------------|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 4 / 12 (33.33%) | 8 / 13 (61.54%) |
| number of deaths (all causes) | 1 | 1 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|----------------|----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchopleural fistula | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |

| | | | |
|---|---------------|----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|----------------|-----------------|
| Lipase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (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 | | | |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (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 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterovirus infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (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 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Ceritinib@560 mg/m2 | Ceritinib@320 mg/m2 | Ceritinib@400 mg/m2 |
|---|------------------------|------------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 3 / 4 (75.00%) | 1 / 5 (20.00%) |
| number of deaths (all causes) | 0 | 2 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |

| | | | |
|---|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchopleural fistula | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|---------------|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |

| | | | |
|---|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (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 |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (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 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental caries | | | |

| | | | |
|---|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|---------------|----------------|---------------|
| disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (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 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterovirus infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|---------------|
| Influenza | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |

| | | | |
|---|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Ceritinib@500 mg/m2 | Fasted+Fed All Subjects | |
|---|---------------------|-------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 42 (50.00%) | 40 / 83 (48.19%) | |
| number of deaths (all causes) | 5 | 12 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 6 / 83 (7.23%) | |
| occurrences causally related to treatment / all | 1 / 7 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchopleural fistula | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 83 (4.82%) | |
| occurrences causally related to treatment / all | 3 / 3 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 4 / 83 (4.82%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 5 / 83 (6.02%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dental caries | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 4 / 83 (4.82%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterovirus infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Septic shock | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Ceritinib@300 mg/m2 | Ceritinib@450 mg/m2 | Ceritinib@510 mg/m2 |
|---|---------------------|---------------------|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 5 (100.00%) | 12 / 12 (100.00%) | 13 / 13 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|---------------------|----------------------|----------------------|
| Tumour pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Vascular disorders | | | |
| Embolism subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Haematoma subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 1 / 13 (7.69%) 1 |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Pallor subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Catheter site pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 12 (16.67%) 2 | 1 / 13 (7.69%) 1 |
| Chest pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 12 (16.67%) 2 | 1 / 13 (7.69%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 3 / 5 (60.00%) 3 | 4 / 12 (33.33%) 6 | 3 / 13 (23.08%) 4 |
| Gait disturbance subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| General physical health deterioration | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 4 / 12 (33.33%) | 6 / 13 (46.15%) |
| occurrences (all) | 5 | 6 | 15 |
| Secretion discharge | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ulcer | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 2 | 7 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea exertional | | | |

| | | | |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 2 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Irritability | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---------------------|-----------------------|-----------------------|
| Restlessness subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 3 | 8 / 12 (66.67%) 13 | 8 / 13 (61.54%) 18 |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 4 | 1 / 13 (7.69%) 1 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 3 | 6 / 12 (50.00%) 10 | 7 / 13 (53.85%) 21 |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 4 / 12 (33.33%) 4 | 0 / 13 (0.00%) 0 |
| Blood bicarbonate decreased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 12 (16.67%) 2 | 0 / 13 (0.00%) 0 |
| Blood creatine increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Blood creatine phosphokinase MB increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Blood creatine phosphokinase increased | | | |

| | | | |
|---------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 4 / 12 (33.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 5 | 5 | 1 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 3 / 13 (23.08%) |
| occurrences (all) | 0 | 3 | 4 |
| Blood magnesium increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 3 / 12 (25.00%) | 3 / 13 (23.08%) |
| occurrences (all) | 0 | 3 | 4 |
| Haemoglobin decreased | | | |

| | | | |
|----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 0 | 2 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 4 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 0 | 1 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Prothrombin time shortened | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Tumour marker increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 12 (16.67%) | 3 / 13 (23.08%) |
| occurrences (all) | 1 | 2 | 3 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|------------------------------|----------------|-----------------|----------------|
| complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |

| | | | |
|--------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 5 (60.00%) | 4 / 12 (33.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 8 | 1 |
| Hypertonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 2 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Migraine | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Syncope | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 3 / 12 (25.00%) | 3 / 13 (23.08%) |
| occurrences (all) | 2 | 4 | 5 |
| Bone marrow disorder | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 0 | 2 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 14 | 1 / 12 (8.33%) 2 | 3 / 13 (23.08%) 6 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 12 (16.67%) 3 | 2 / 13 (15.38%) 2 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| External ear inflammation subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Hypoacusis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Eye swelling subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Ocular discomfort subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 5 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Abdominal pain | | | |

| | | | |
|-----------------------------|----------------|-------------------|------------------|
| subjects affected / exposed | 3 / 5 (60.00%) | 6 / 12 (50.00%) | 6 / 13 (46.15%) |
| occurrences (all) | 6 | 17 | 12 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Anal incontinence | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Anal inflammation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 2 / 12 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all) | 4 | 3 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | 12 / 12 (100.00%) | 10 / 13 (76.92%) |
| occurrences (all) | 11 | 30 | 21 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Haematochezia | | | |

| | | | |
|--|----------------|------------------|-------------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 8 / 12 (66.67%) | 10 / 13 (76.92%) |
| occurrences (all) | 3 | 8 | 20 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | 10 / 12 (83.33%) | 13 / 13 (100.00%) |
| occurrences (all) | 11 | 25 | 33 |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Eczema | | | |

| | | | |
|-----------------------------|---------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 2 | 2 |
| Rash | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 3 / 12 (25.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 3 | 1 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Swelling face | | | |

| | | | |
|---|---------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 2 | 0 / 13 (0.00%) 0 |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Endocrine disorders Delayed puberty subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 13 (15.38%) 2 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 2 | 1 / 13 (7.69%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 2 / 12 (16.67%) 3 | 0 / 13 (0.00%) 0 |
| Groin pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 12 (8.33%) 1 | 1 / 13 (7.69%) 1 |
| Joint range of motion decreased | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 4 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 5 / 12 (41.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |
| Torticollis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Bacterial vulvovaginitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 3 | 1 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-------------------------------|----------------|-----------------|-----------------|
| Ear infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital candidiasis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Human herpesvirus 6 infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Mycoplasma infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 6 | 1 | 3 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |

| | | | |
|------------------------------------|----------------|-----------------|-----------------|
| Sinusitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 12 (16.67%) | 3 / 13 (23.08%) |
| occurrences (all) | 2 | 3 | 8 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Varicella | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 4 / 12 (33.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 2 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypermagnesaemia | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 2 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 6 | 2 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 2 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 2 / 12 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 4 | 2 | 1 |
| Obesity | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| Non-serious adverse events | Ceritinib@560 mg/m2 | Ceritinib@320 mg/m2 | Ceritinib@400 mg/m2 |
|---|------------------------|------------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 4 / 4 (100.00%) | 5 / 5 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |

| | | | |
|--|-----------------|----------------|----------------|
| Embolism | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pallor | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 3 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza like illness | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Secretion discharge | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ulcer | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Emphysema | | | |

| | | | |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Irritability | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 2 (100.00%) 2 | 3 / 4 (75.00%) 5 | 2 / 5 (40.00%) 2 |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 2 (100.00%) 2 | 3 / 4 (75.00%) 3 | 1 / 5 (20.00%) 1 |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 |
| Blood bicarbonate decreased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 |
| Blood creatine increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood creatine phosphokinase MB increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Blood creatinine increased | | | |

| | | | |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood magnesium increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 2 / 4 (50.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 1 | 2 | 3 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lipase increased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prothrombin time shortened | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tumour marker increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |

| | | | |
|---|--------------------|--------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hand fracture subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Muscle injury subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Cardiac disorders Left ventricular dysfunction subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Pericardial effusion subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Dysaesthesia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Headache | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 4 (50.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Hypertonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 3 / 4 (75.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Bone marrow disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------------|---------------------|--------------------|
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 2 (100.00%) 2 | 2 / 4 (50.00%) 3 | 0 / 5 (0.00%) 0 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| External ear inflammation subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hypoacusis subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Eye swelling subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Ocular discomfort subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Abdominal pain | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 2 (100.00%) | 2 / 4 (50.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 7 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal incontinence | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal inflammation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 2 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 2 / 4 (50.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 4 | 7 | 3 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematochezia | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 2 / 4 (50.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 3 | 4 | 3 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 4 / 4 (100.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 4 | 7 | 3 |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin irritation | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Swelling face | | | |

| | | | |
|---|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Delayed puberty | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint range of motion decreased | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Torticollis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Bacterial vulvovaginitis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-------------------------------|---------------|----------------|---------------|
| Ear infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital candidiasis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Human herpesvirus 6 infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mycoplasma infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|------------------------------------|-----------------|----------------|----------------|
| Sinusitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Varicella | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypermagnesaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Obesity | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Ceritinib@500 mg/m2 | Fasted+Fed All Subjects | |
|--|------------------------|----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 42 (100.00%) | 83 / 83 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |

| | | | |
|--|-----------------|------------------|--|
| Embolism | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences (all) | 0 | 2 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 2 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Pallor | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) | |
| occurrences (all) | 3 | 3 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 42 (21.43%) | 10 / 83 (12.05%) | |
| occurrences (all) | 11 | 12 | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 3 / 83 (3.61%) | |
| occurrences (all) | 0 | 3 | |
| Chest pain | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 11 / 83 (13.25%) | |
| occurrences (all) | 6 | 13 | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 42 (21.43%) | 22 / 83 (26.51%) | |
| occurrences (all) | 14 | 31 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences (all) | 0 | 2 | |
| Influenza like illness | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 2 | 2 / 83 (2.41%) 3 | |
| Malaise subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 2 / 83 (2.41%) 2 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 3 | 4 / 83 (4.82%) 5 | |
| Pyrexia subjects affected / exposed occurrences (all) | 20 / 42 (47.62%) 49 | 35 / 83 (42.17%) 77 | |
| Secretion discharge subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 3 / 83 (3.61%) 3 | |
| Ulcer subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Cough subjects affected / exposed occurrences (all) | 8 / 42 (19.05%) 16 | 13 / 83 (15.66%) 27 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 5 | 6 / 83 (7.23%) 7 | |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Emphysema | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 83 (4.82%) | |
| occurrences (all) | 3 | 5 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 83 (3.61%) | |
| occurrences (all) | 1 | 3 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 5 / 83 (6.02%) | |
| occurrences (all) | 4 | 7 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 83 (3.61%) | |
| occurrences (all) | 2 | 3 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 2 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 4 / 83 (4.82%) | |
| occurrences (all) | 5 | 8 | |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 83 (3.61%) | |
| occurrences (all) | 2 | 4 | |
| Irritability | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|------------------------|-------------------------|--|
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 30 / 42 (71.43%) 72 | 54 / 83 (65.06%) 115 | |
| Amylase increased subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 5 | 6 / 83 (7.23%) 11 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 28 / 42 (66.67%) 74 | 48 / 83 (57.83%) 114 | |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 4 | 10 / 83 (12.05%) 10 | |
| Blood bicarbonate decreased subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 2 / 83 (2.41%) 2 | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 9 | 8 / 83 (9.64%) 12 | |
| Blood creatine increased subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 4 | 3 / 83 (3.61%) 4 | |
| Blood creatine phosphokinase MB increased subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Blood creatinine increased | | | |

| | | |
|---------------------------------------|------------------|------------------|
| subjects affected / exposed | 11 / 42 (26.19%) | 18 / 83 (21.69%) |
| occurrences (all) | 17 | 28 |
| Blood glucose increased | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Blood lactate dehydrogenase increased | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 11 / 83 (13.25%) |
| occurrences (all) | 5 | 13 |
| Blood magnesium increased | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 4 | 4 |
| Blood pressure increased | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Blood urea increased | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 6 | 6 |
| Blood uric acid increased | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 4 / 83 (4.82%) |
| occurrences (all) | 3 | 4 |
| C-reactive protein increased | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 6 / 83 (7.23%) |
| occurrences (all) | 4 | 6 |
| Electrocardiogram QT prolonged | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 83 (3.61%) |
| occurrences (all) | 1 | 3 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 14 / 42 (33.33%) | 26 / 83 (31.33%) |
| occurrences (all) | 21 | 34 |
| Haemoglobin decreased | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 3 |
| Lipase increased | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 6 / 42 (14.29%) | 9 / 83 (10.84%) | |
| occurrences (all) | 9 | 12 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 83 (4.82%) | |
| occurrences (all) | 5 | 10 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 5 / 83 (6.02%) | |
| occurrences (all) | 2 | 6 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 83 (3.61%) | |
| occurrences (all) | 1 | 4 | |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Prothrombin time shortened | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences (all) | 0 | 2 | |
| Tumour marker increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 13 / 83 (15.66%) | |
| occurrences (all) | 7 | 14 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 4 / 83 (4.82%) | |
| occurrences (all) | 1 | 5 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 2 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Fall subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 2 / 83 (2.41%) 2 | |
| Hand fracture subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Muscle injury subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Cardiac disorders Left ventricular dysfunction subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 2 / 83 (2.41%) 2 | |
| Pericardial effusion subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 2 / 83 (2.41%) 2 | |
| Tachycardia subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | 4 / 83 (4.82%) 4 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 3 | 5 / 83 (6.02%) 6 | |
| Dysaesthesia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 2 / 83 (2.41%) 2 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Headache | | | |

| | | | |
|--------------------------------------|------------------|------------------|--|
| subjects affected / exposed | 8 / 42 (19.05%) | 19 / 83 (22.89%) | |
| occurrences (all) | 20 | 35 | |
| Hypertonia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 2 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Tremor | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 83 (3.61%) | |
| occurrences (all) | 1 | 3 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 11 / 42 (26.19%) | 22 / 83 (26.51%) | |
| occurrences (all) | 14 | 31 | |
| Bone marrow disorder | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences (all) | 0 | 2 | |
| Leukopenia | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 8 / 83 (9.64%) | |
| occurrences (all) | 7 | 10 | |

| | | | |
|--|------------------------|------------------------|--|
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Neutropenia subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 23 | 10 / 83 (12.05%) 45 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 11 / 42 (26.19%) 16 | 19 / 83 (22.89%) 26 | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 4 | 4 / 83 (4.82%) 5 | |
| External ear inflammation subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Hypoacusis subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Eye swelling subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Ocular discomfort subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 2 / 83 (2.41%) 6 | |
| Abdominal pain | | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 22 / 42 (52.38%) | 42 / 83 (50.60%) |
| occurrences (all) | 56 | 101 |
| Abdominal pain upper | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 7 / 83 (8.43%) |
| occurrences (all) | 3 | 8 |
| Anal fissure | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Anal incontinence | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Anal inflammation | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Constipation | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 14 / 83 (16.87%) |
| occurrences (all) | 4 | 18 |
| Diarrhoea | | |
| subjects affected / exposed | 32 / 42 (76.19%) | 65 / 83 (78.31%) |
| occurrences (all) | 93 | 169 |
| Dyspepsia | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 6 / 83 (7.23%) |
| occurrences (all) | 6 | 8 |
| Flatulence | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 4 / 83 (4.82%) |
| occurrences (all) | 1 | 4 |
| Gastrointestinal disorder | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Gingival pain | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Haematemesis | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Haematochezia | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 21 / 42 (50.00%) | 47 / 83 (56.63%) | |
| occurrences (all) | 32 | 73 | |
| Odynophagia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) | |
| occurrences (all) | 3 | 3 | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 5 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 6 / 83 (7.23%) | |
| occurrences (all) | 3 | 6 | |
| Vomiting | | | |
| subjects affected / exposed | 36 / 42 (85.71%) | 72 / 83 (86.75%) | |
| occurrences (all) | 72 | 155 | |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences (all) | 2 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 83 (4.82%) | |
| occurrences (all) | 2 | 4 | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 83 (3.61%) | |
| occurrences (all) | 1 | 3 | |
| Eczema | | | |

| | | |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 5 | 5 |
| Erythema | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 4 / 83 (4.82%) |
| occurrences (all) | 6 | 6 |
| Night sweats | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 3 | 3 |
| Pain of skin | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Pruritus | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 7 / 83 (8.43%) |
| occurrences (all) | 1 | 7 |
| Rash | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 8 / 83 (9.64%) |
| occurrences (all) | 10 | 15 |
| Rash erythematous | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Rash maculo-papular | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 5 / 83 (6.02%) |
| occurrences (all) | 1 | 5 |
| Skin exfoliation | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Skin hyperpigmentation | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Skin irritation | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Skin lesion | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Swelling face | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 2 / 83 (2.41%) 2 | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 2 | |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Endocrine disorders Delayed puberty subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 2 / 83 (2.41%) 2 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 4 / 83 (4.82%) 5 | |
| Back pain subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 4 | 6 / 83 (7.23%) 6 | |
| Bone pain subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | 6 / 83 (7.23%) 7 | |
| Groin pain subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 83 (3.61%) 3 | |
| Joint range of motion decreased | | | |

| | | | |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 2 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 83 (3.61%) | |
| occurrences (all) | 2 | 3 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 5 / 83 (6.02%) | |
| occurrences (all) | 3 | 8 | |
| Neck pain | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 83 (3.61%) | |
| occurrences (all) | 2 | 4 | |
| Pain in extremity | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 13 / 83 (15.66%) | |
| occurrences (all) | 5 | 14 | |
| Torticollis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Bacterial vulvovaginitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 83 (3.61%) | |
| occurrences (all) | 2 | 3 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 5 / 83 (6.02%) | |
| occurrences (all) | 3 | 7 | |
| Device related infection | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) | |
| occurrences (all) | 5 | 5 | |

| | | |
|-------------------------------|-----------------|------------------|
| Ear infection | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 3 |
| Gastroenteritis | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 4 / 83 (4.82%) |
| occurrences (all) | 5 | 5 |
| Genital candidiasis | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 2 |
| Human herpesvirus 6 infection | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Influenza | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 83 (4.82%) |
| occurrences (all) | 2 | 8 |
| Molluscum contagiosum | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Mycoplasma infection | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Nasopharyngitis | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 10 / 83 (12.05%) |
| occurrences (all) | 4 | 16 |
| Oral herpes | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Pharyngitis | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Pneumonia | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 83 (3.61%) |
| occurrences (all) | 5 | 5 |
| Rhinitis | | |
| subjects affected / exposed | 8 / 42 (19.05%) | 11 / 83 (13.25%) |
| occurrences (all) | 12 | 15 |

| | | | |
|------------------------------------|------------------|------------------|--|
| Sinusitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 42 (19.05%) | 15 / 83 (18.07%) | |
| occurrences (all) | 20 | 34 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 3 / 83 (3.61%) | |
| occurrences (all) | 0 | 5 | |
| Varicella | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 2 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 2 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 83 (2.41%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 16 / 42 (38.10%) | 26 / 83 (31.33%) | |
| occurrences (all) | 17 | 29 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 3 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 2 | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 4 | |
| Hypermagnesaemia | | | |

| | | | |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 5 / 83 (6.02%) | |
| occurrences (all) | 4 | 5 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 4 / 83 (4.82%) | |
| occurrences (all) | 1 | 5 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | 12 / 83 (14.46%) | |
| occurrences (all) | 9 | 19 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 5 / 83 (6.02%) | |
| occurrences (all) | 4 | 6 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 7 / 83 (8.43%) | |
| occurrences (all) | 3 | 8 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 8 / 83 (9.64%) | |
| occurrences (all) | 4 | 12 | |
| Obesity | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 14 March 2013 | <p>The following changes were requested by a Health Authority: In order to clarify the eligibility criteria in the protocol, a detailed definition of "a genetic alteration of ALK" has been added to the inclusion criteria.</p> <p>Due to the observation that ceritinib use is sometimes associated with hypophosphatemia, patients with abnormalities of phosphate as well as potassium, calcium or magnesium > CTCAE grade 1 are excluded from the study. The table defining dose-limiting toxicities was reorganized to clarify that any adverse event of CTCAE grade 3 or higher is a DLT, except as noted in the table.</p> <p>Due to the possibility that taking ceritinib mixed with a small amount of food may affect its bioavailability, the protocol has been modified to require that all patients take ceritinib with a small amount of food. If patients can swallow intact capsules, they must eat 1-2 tablespoons (15-30 mL) of food, such as apple sauce or non-fat yogurt at the time that they take ceritinib. If patients open the capsules, the contents are mixed with a food carrier, such as apple sauce or non-fat yogurt (or other carriers as defined in the separate instructions for patients who cannot swallow capsules). This prevented unexpected differences in bioavailability between those patients who swallow intact capsules and those who opened the capsules.</p> |
| 27 September 2013 | <p>The following changes were requested by Health Authorities:</p> <p>To address the management of QTc prolongation separately from the broader array of DLTs a specific approach including a detailed monitoring plan, need for physician evaluation, and recommendations for dose reduction or permanent discontinuation.</p> <p>Cases of pneumonitis/interstitial lung disease (ILD) have been reported with ceritinib in patients treated at the 750 mg dose level. Most cases improved or resolved with interruption of ceritinib and treatment with antibiotics and/or steroids. Fatal outcome of treatment-related pneumonitis was reported. Exclusion criteria, the definition of dose limiting toxicity, and the guidance for dose modification have been amended to address this newly observed risk</p> |
| 15 July 2014 | <p>The protocol was modified to include a fed state (low-fat light snack) dose escalation part following the determination of the fasted MTD/RDE. Further expansion at the fed MTD/RDE was allowed if the safety, PK or efficacy suggested that administering ceritinib with food was preferred. The age range in the inclusion criteria has been changed to 'up to 18' to make it clear that patients were eligible until they turn 18 years of age.</p> |
| 13 May 2015 | <p>A consistent approach was implemented across ongoing studies with ceritinib to monitor and manage safety signals identified as the clinical experience with ceritinib has grown. Specifically, changes were made that addressed hepatic toxicity, pancreatitis and pneumonitis.</p> |
| 26 February 2016 | <p>The primary purpose of this amendment was to clarify the ceritinib dose modification recommendations, the guidelines for follow up of toxicities to ceritinib (including follow up evaluations for hepatic toxicities and work up guidelines for potential drug induced liver injury (DILI) cases) and the use of concomitant medications in order to optimize the patient safety. Furthermore, this amendment provided updated parameters for study visits for patients who were on study drug for more than 14 cycles. This was done in an effort to decrease the burden on the patient after a set number of cycles on study drug.</p> <p>In addition, the definition of highly effective contraception and the time period for using it have been updated, as well as the reporting period for pregnancy that has been revised to 3 months.</p> |

| | |
|-------------------|---|
| 30 September 2016 | <p>The primary purpose of this amendment was to revise the dose reduction steps for ceritinib. The primary purpose of this amendment was to revise the dose reduction steps for ceritinib. Considering the recommended doses established for fed and fasted state were similar, the dose reduction schedule was revised to be applicable for both states.</p> <p>In addition, the schedule of assessments was revised to reduce frequency of on-site visits after cycle 16: on-site visits on day 1 of odd numbered cycles are replaced by phone calls and local laboratory tests for safety assessments</p> <p>Moreover, the pre-dose PK sample and the post-dose ECGs collection at Cycle 1 Day 1 have been removed in the expansion phase as they were no longer required at this time point as no correlation is planned in the expansion.</p> |
| 24 January 2017 | <p>The primary purpose of this amendment was to address Health Authorities' concerns regarding the cardiac safety monitoring conducted until Cycle 6 only and not afterwards for patient who remain on treatment, and the recent changes at Cycle 1 Day 1 (ECG monitoring at 4 and 6 hours post first dose of study drug) for the patients to be treated in the expansion phase of the study. Novartis decided to strengthen the cardiac safety monitoring: all patients were monitored with an ECG at Cycle 1 Day 1 (4-h post dose and 6-h post dose), and at each first day of every cycle of treatment. The ECG collection was expanded throughout the entire treatment duration. This was done in alignment with the ceritinib cardiovascular safety monitoring recommendations.</p> <p>In addition, guidelines for dose modification in case of Grade 3 transaminases elevation are clarified, allowing patients to stay in the study in case of a re-occurrence of Grade 3 ALT or AST elevation after a dose reduction as allowed across the ceritinib development program in adults patients. This was to avoid unnecessary withdrawal of patients who continued to derive clinical benefit from ceritinib.</p> <p>The guidelines in relation to concomitant medications use are also clarified to optimize the patient's safety.</p> <p>Moreover, ALK status inclusion criterion was clarified and it was specified that 15% threshold for rearrangement was applicable only when assessed by FISH. Furthermore the ALK tyrosine kinase domain (TKD) mutation inclusion criterion was simplified.</p> |
| 18 May 2018 | <p>The main purpose of this global amendment was to allow patients who were still deriving clinical benefit from study treatment as per the investigator to be transitioned to a separate rollover study or another option for continued treatment with ceritinib (i.e. managed access program), as soon as they become available. The end of study would occur once:</p> <p>All patients have discontinued study treatment and completed the required Study Evaluation Completion follow-up visit, or</p> <p>All patients have died, been lost to follow-up, have withdrawn consent, or the last patient has been enrolled into a separate rollover study (or other option for continued study treatment), whichever comes first</p> <p>As per original protocol, a primary analysis and CSR were planned after all patients had completed at least 6 cycles of treatment or discontinued the study. Given interim data presented previously, and at the time of this amendment all patients already completed at least 6 cycles of treatment and were allowed to transition into a separate rollover study (or other options for continued study treatment access), a single final analysis/CSR was planned once the end of study criteria are met.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: