



Clinical trial results:

A Phase 1/2 Study of ARQ 087 in Adult Subjects with Advanced Solid Tumors with FGFR Genetic Alterations, Including Intrahepatic Cholangiocarcinoma with FGFR2 Gene Fusion

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-001443-36 |
| Trial protocol | IT |
| Global end of trial date | 28 August 2018 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 |
| This version publication date | 08 September 2021 |
| First version publication date | 08 September 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | ARQ 087-101 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01752920 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Basilea Pharmaceutica International Ltd. |
| Sponsor organisation address | Grenzacherstrasse 487, Basel, Switzerland, 4005 |
| Public contact | Head of Development, Basilea Pharmaceutica International Ltd., +41 61 606 12 25, stephan.braun@basilea.com |
| Scientific contact | Head of Development, Basilea Pharmaceutica International Ltd., +41 61 606 12 25, stephan.braun@basilea.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 January 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 August 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 August 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this first-in-humans study was to assess the safety and tolerability of ARQ 087 in patients with advanced solid tumors (Part 1; Dose Escalation/Food-effect Cohorts) or with advanced solid tumors with FGFR genetic aberrations, including iCCA with FGFR2 gene fusion (Part 2; Expanded Cohort, signal finding).

Protection of trial subjects:

No additional pain or distress was caused by the use of the investigational product.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 10 December 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 101 |
| Country: Number of subjects enrolled | Italy: 18 |
| Worldwide total number of subjects | 119 |
| EEA total number of subjects | 18 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 66 |
| From 65 to 84 years | 53 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 12 study centers, 8 in the US and 4 in Italy. 119 patients were recruited between December 2012 and January 2017.

Pre-assignment

Screening details:

A fresh core needle biopsy or fine needle aspiration could be collected during the screening period if archival tumor tissue biopsy samples were not available.

Period 1

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

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Low Dose Group |

Arm description:

Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

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

Dosage and administration details:

Derazantinib was administered orally at dose levels from 25 mg every other day (QOD) - 200 mg daily (QD) on a 28-day schedule.

| | |
|------------------|-------------------|
| Arm title | Middle Dose Group |
|------------------|-------------------|

Arm description:

Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

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

Dosage and administration details:

Derazantinib was administered orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule.

| | |
|------------------|-----------------|
| Arm title | High Dose Group |
|------------------|-----------------|

Arm description:

Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

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

Dosage and administration details:

Derazantinib was administered orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule.

| | |
|------------------|-----------------------|
| Arm title | Expanded Cohort Group |
|------------------|-----------------------|

Arm description:

Patients who received derazantinib orally at the recommended Phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

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

Dosage and administration details:

Derazantinib was administered orally at the recommended phase 2 dose of 300 mg QD on a 28-day schedule.

| Number of subjects in period 1 | Low Dose Group | Middle Dose Group | High Dose Group |
|---------------------------------------|----------------|-------------------|-----------------|
| Started | 29 | 13 | 19 |
| Completed | 0 | 0 | 0 |
| Not completed | 29 | 13 | 19 |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject | - | 1 | - |
| Radiographic disease progression | 20 | 7 | 12 |
| Adverse event, non-fatal | 1 | - | 5 |
| Other | 1 | 1 | 1 |
| Clinical disease progression | 6 | 4 | 1 |
| Study terminated by sponsor | - | - | - |

| Number of subjects in period 1 | Expanded Cohort Group |
|---------------------------------------|-----------------------|
| Started | 58 |
| Completed | 0 |
| Not completed | 58 |
| Physician decision | 2 |
| Consent withdrawn by subject | 1 |
| Radiographic disease progression | 29 |
| Adverse event, non-fatal | 10 |

| | |
|------------------------------|----|
| Other | 2 |
| Clinical disease progression | 13 |
| Study terminated by sponsor | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Low Dose Group |
|-----------------------|----------------|

Reporting group description:

Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

| | |
|-----------------------|-------------------|
| Reporting group title | Middle Dose Group |
|-----------------------|-------------------|

Reporting group description:

Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

| | |
|-----------------------|-----------------|
| Reporting group title | High Dose Group |
|-----------------------|-----------------|

Reporting group description:

Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

| | |
|-----------------------|-----------------------|
| Reporting group title | Expanded Cohort Group |
|-----------------------|-----------------------|

Reporting group description:

Patients who received derazantinib orally at the recommended Phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

| Reporting group values | Low Dose Group | Middle Dose Group | High Dose Group |
|---------------------------|----------------|-------------------|-----------------|
| Number of subjects | 29 | 13 | 19 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age < 65 | 19 | 4 | 8 |
| Age ≥ 65 | 10 | 9 | 11 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 17 | 9 | 11 |
| Male | 12 | 4 | 8 |
| Race | | | |
| Units: Subjects | | | |
| Black or African American | 3 | 1 | 2 |
| White | 24 | 11 | 16 |
| Other | 2 | 1 | 1 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 3 | 1 | 3 |
| Not Hispanic or Latino | 26 | 12 | 16 |

| Reporting group values | Expanded Cohort Group | Total | |
|------------------------|-----------------------|-------|--|
| Number of subjects | 58 | 119 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age < 65 | 35 | 66 | |

| | | | |
|----------|----|----|--|
| Age >=65 | 23 | 53 | |
|----------|----|----|--|

| | | | |
|---------------------------------------|----|-----|--|
| Gender categorical Units: Subjects | | | |
| Female | 32 | 69 | |
| Male | 26 | 50 | |
| Race Units: Subjects | | | |
| Black or African American | 3 | 9 | |
| White | 54 | 105 | |
| Other | 1 | 5 | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 2 | 9 | |
| Not Hispanic or Latino | 56 | 110 | |

End points

End points reporting groups

| | |
|---|-----------------------|
| Reporting group title | Low Dose Group |
| Reporting group description: Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria. | |
| Reporting group title | Middle Dose Group |
| Reporting group description: Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria. | |
| Reporting group title | High Dose Group |
| Reporting group description: Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria. | |
| Reporting group title | Expanded Cohort Group |
| Reporting group description: Patients who received derazantinib orally at the recommended Phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria. | |

Primary: Incidence of adverse events

| | |
|--|--|
| End point title | Incidence of adverse events ^[1] |
| End point description: Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. | |
| End point type | Primary |
| End point timeframe: Adverse events were collected and reported from the time of receiving first dose of derazantinib to the end of study assessment and follow-up period | |

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: The primary objective of this study was to evaluate the safety and tolerability of derazantinib and the study was not powered for formal statistical analysis.

| End point values | Low Dose Group | Middle Dose Group | High Dose Group | Expanded Cohort Group |
|-----------------------------|-----------------|-------------------|-----------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 13 | 19 | 58 |
| Units: Number of subjects | | | | |
| TEAE Grade 1 | 3 | 1 | 1 | 11 |
| TEAE Grade 2 | 14 | 5 | 3 | 14 |
| TEAE Grade 3 | 9 | 6 | 13 | 24 |
| TEAE Grade 4 | 0 | 1 | 0 | 4 |
| TEAE Grade 5 | 2 | 0 | 2 | 5 |
| no TEAE | 1 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response (ORR) per RECIST 1.1

| | |
|-----------------|---|
| End point title | Objective tumor response (ORR) per RECIST 1.1 |
|-----------------|---|

End point description:

The number of patients with an objective tumor response, which included those with either a complete response (CR) or a partial response (PR). The objective response rate (ORR) was defined as the proportion of patients with a CR or PR.

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

End point timeframe:

At the End of Treatment visit (7 [+3] days after the last dose of derazantinib)

| End point values | Low Dose Group | Middle Dose Group | High Dose Group | Expanded Cohort Group |
|-----------------------------|-----------------|-------------------|-----------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 13 | 19 | 58 |
| Units: Number of subjects | 0 | 0 | 1 | 5 |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) per RECIST 1.1

| | |
|-----------------|---|
| End point title | Disease control rate (DCR) per RECIST 1.1 |
|-----------------|---|

End point description:

The number of patients with tumor disease control, which included those with either a complete or partial tumor response, or a stable disease (SD). The disease control rate (DCR) was defined as the proportion of patients with CR, PR or SD.

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

End point timeframe:

At the End of Treatment visit (7 [+3] days after the last dose of derazantinib)

| End point values | Low Dose Group | Middle Dose Group | High Dose Group | Expanded Cohort Group |
|-----------------------------|-----------------|-------------------|-----------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 13 | 19 | 58 |
| Units: Number of subjects | 8 | 4 | 7 | 32 |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

| | |
|-----------------|---------------------------------|
| End point title | Progression-free survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS was calculated as the time from the date of first dose until radiographic disease progression or death from any cause.

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

End point timeframe:

At the End of Treatment visit (7 [+3] days after the last dose of derazantinib)

| End point values | Low Dose Group | Middle Dose Group | High Dose Group | Expanded Cohort Group |
|----------------------------------|------------------|--------------------|-------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 13 | 19 | 58 |
| Units: weeks | | | | |
| median (confidence interval 95%) | 8.3 (6.3 to 9.3) | 15.3 (6.7 to 22.1) | 8.1 (6.7 to 23.9) | 17.4 (7.9 to 24.9) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study medication up to 30 days after the last administration.

Adverse event reporting additional description:

Treatment-emergent adverse events and serious adverse events

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Low Dose Group |
|-----------------------|----------------|

Reporting group description:

Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.

| | |
|-----------------------|-------------------|
| Reporting group title | Middle Dose Group |
|-----------------------|-------------------|

Reporting group description:

Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.

| | |
|-----------------------|-----------------|
| Reporting group title | High Dose Group |
|-----------------------|-----------------|

Reporting group description:

Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.

| | |
|-----------------------|-----------------------|
| Reporting group title | Expanded Cohort Group |
|-----------------------|-----------------------|

Reporting group description:

Patients who received derazantinib orally at the recommended phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.

| Serious adverse events | Low Dose Group | Middle Dose Group | High Dose Group |
|---|-----------------|-------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 29 (31.03%) | 2 / 13 (15.38%) | 6 / 19 (31.58%) |
| number of deaths (all causes) | 2 | 0 | 2 |
| number of deaths resulting from adverse events | 2 | 0 | 2 |
| Investigations | | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram abnormal | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| 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 | | | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord injury cervical | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 |
| Disease progression | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| 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 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| 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 | | | |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Odynophagia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| 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 obstruction | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| 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 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| 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 | | | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 |
| Pyelonephritis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (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 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| 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 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (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 |

| Serious adverse events | Expanded Cohort Group | | |
|--|-----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 58 (27.59%) | | |
| number of deaths (all causes) | 9 | | |
| number of deaths resulting from adverse events | 5 | | |
| Investigations | | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord injury cervical | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disease progression | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Low Dose Group | Middle Dose Group | High Dose Group |
|---|------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 29 (96.55%) | 13 / 13 (100.00%) | 19 / 19 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertension | | | |

| | | | |
|--|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 4 / 19 (21.05%) |
| occurrences (all) | 0 | 0 | 4 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Discomfort | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 18 / 29 (62.07%) | 8 / 13 (61.54%) | 11 / 19 (57.89%) |
| occurrences (all) | 24 | 14 | 18 |
| Feeling abnormal | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 0 | 0 | 2 |
| Malaise | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 1 | 2 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 1 | 1 |
| Pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Performance status decreased | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 4 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 4 | 0 | 2 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 6 | 0 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypoxia | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 4 |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal mucosal disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 2 | 0 | 2 |
| Psychiatric disorders | | | |

| | | | |
|--|-----------------|-----------------|------------------|
| Anxiety | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 3 / 13 (23.08%) | 2 / 19 (10.53%) |
| occurrences (all) | 5 | 3 | 3 |
| Depression | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 4 | 0 | 1 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 13 (7.69%) | 2 / 19 (10.53%) |
| occurrences (all) | 2 | 1 | 2 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 3 / 13 (23.08%) | 4 / 19 (21.05%) |
| occurrences (all) | 2 | 3 | 6 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 7 / 13 (53.85%) | 10 / 19 (52.63%) |
| occurrences (all) | 10 | 10 | 14 |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | 2 / 13 (15.38%) | 1 / 19 (5.26%) |
| occurrences (all) | 8 | 2 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 1 / 13 (7.69%) | 4 / 19 (21.05%) |
| occurrences (all) | 4 | 1 | 4 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 2 / 13 (15.38%) | 3 / 19 (15.79%) |
| occurrences (all) | 6 | 2 | 3 |
| Blood thyroid stimulating hormone | | | |

| | | | |
|--|----------------|----------------|-----------------|
| increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 3 / 19 (15.79%) |
| occurrences (all) | 1 | 0 | 3 |
| Breath sounds abnormal | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 0 | 0 | 2 |
| Electrocardiogram QT interval abnormal | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Visual acuity tests abnormal | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 0 | 0 | 2 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Contusion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 1 | 1 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 3 / 19 (15.79%) |
| occurrences (all) | 1 | 1 | 4 |
| Head injury | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Joint injury subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Rib fracture subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Scratch subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Congenital, familial and genetic disorders Ichthyosis subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Cardiac disorders Cardiomegaly subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Pericardial effusion subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Tachycardia subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Nervous system disorders Ataxia subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Balance disorder subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Burning sensation subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 2 |
| Clumsiness | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 13 (7.69%) | 5 / 19 (26.32%) |
| occurrences (all) | 2 | 1 | 11 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 13 (15.38%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 2 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 3 / 13 (23.08%) | 3 / 19 (15.79%) |
| occurrences (all) | 3 | 3 | 3 |
| Head discomfort | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 3 / 19 (15.79%) |
| occurrences (all) | 1 | 1 | 5 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 1 | 0 | 2 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 3 / 13 (23.08%) | 0 / 19 (0.00%) |
| occurrences (all) | 12 | 4 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 0 | 1 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 3 / 19 (15.79%) |
| occurrences (all) | 0 | 0 | 3 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Hearing impaired | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 13 (15.38%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vision blurred | | | |

| | | | |
|---|-----------------------|----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Visual impairment subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 4 | 1 / 13 (7.69%) 1 | 1 / 19 (5.26%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 13 (15.38%) 2 | 1 / 19 (5.26%) 2 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 3 / 13 (23.08%) 5 | 0 / 19 (0.00%) 0 |
| Ascites subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Cheilitis subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 5 / 29 (17.24%) 5 | 4 / 13 (30.77%) 5 | 7 / 19 (36.84%) 9 |
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 29 (20.69%) 11 | 5 / 13 (38.46%) 5 | 9 / 19 (47.37%) 10 |
| Dry mouth subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 1 / 13 (7.69%) 1 | 6 / 19 (31.58%) 8 |
| Dyspepsia subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 0 / 13 (0.00%) 0 | 3 / 19 (15.79%) 3 |

| | | | |
|----------------------------------|------------------|-----------------|------------------|
| Flatulence | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Frequent bowel movements | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 13 (15.38%) | 3 / 19 (15.79%) |
| occurrences (all) | 0 | 2 | 4 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Lip disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lip pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 14 / 29 (48.28%) | 8 / 13 (61.54%) | 13 / 19 (68.42%) |
| occurrences (all) | 18 | 14 | 15 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral dysaesthesia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|------------------|-----------------|-----------------|
| Stomatitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Tongue disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 10 / 29 (34.48%) | 2 / 13 (15.38%) | 7 / 19 (36.84%) |
| occurrences (all) | 11 | 5 | 7 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 1 | 1 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 13 (15.38%) | 5 / 19 (26.32%) |
| occurrences (all) | 2 | 2 | 6 |
| Erythema | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Night sweats | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Onychomadesis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Photosensitivity reaction | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 0 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Scab | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Scar | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 2 / 19 (10.53%) |
| occurrences (all) | 0 | 1 | 3 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|--|----------------------|---------------------|----------------------|
| Micturition frequency decreased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Pollakiuria subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Proteinuria subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 5 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 13 (7.69%) 1 | 2 / 19 (10.53%) 3 |
| Muscle twitching subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 13 (7.69%) 1 | 0 / 19 (0.00%) 0 |
| Infections and infestations Candidiasis subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 13 (7.69%) 1 | 1 / 19 (5.26%) 1 |

| | | | |
|------------------------------------|------------------|-----------------|-----------------|
| Cystitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 1 | 1 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 2 | 0 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 1 | 0 | 2 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 12 / 29 (41.38%) | 3 / 13 (23.08%) | 6 / 19 (31.58%) |
| occurrences (all) | 14 | 6 | 8 |
| Dehydration | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 13 (0.00%) | 4 / 19 (21.05%) |
| occurrences (all) | 2 | 0 | 5 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 3 / 19 (15.79%) |
| occurrences (all) | 0 | 0 | 3 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 13 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 3 / 13 (23.08%) | 1 / 19 (5.26%) |
| occurrences (all) | 10 | 4 | 1 |
| Hypochloraemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 3 / 13 (23.08%) | 2 / 19 (10.53%) |
| occurrences (all) | 3 | 4 | 3 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 1 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 13 (0.00%) | 3 / 19 (15.79%) |
| occurrences (all) | 2 | 0 | 4 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 13 (7.69%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 13 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |

| Non-serious adverse events | Expanded Cohort Group | | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 58 / 58 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour pain subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | | |
| Vascular disorders Flushing subjects affected / exposed occurrences (all) Haematoma subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 0 / 58 (0.00%) 0 5 / 58 (8.62%) 5 0 / 58 (0.00%) 0 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Discomfort subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Feeling abnormal subjects affected / exposed occurrences (all) | 13 / 58 (22.41%) 26 4 / 58 (6.90%) 4 0 / 58 (0.00%) 0 26 / 58 (44.83%) 40 0 / 58 (0.00%) 0 | | |

| | | | |
|---|-----------------|--|--|
| Feeling hot | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 5 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 2 | | |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | | |
| occurrences (all) | 9 | | |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Cough | | | |
| subjects affected / exposed | 7 / 58 (12.07%) | | |
| occurrences (all) | 7 | | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Epistaxis | | | |
| subjects affected / exposed | 8 / 58 (13.79%) | | |
| occurrences (all) | 9 | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Nasal dryness | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Nasal mucosal disorder | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|------------------------|--|--|
| Respiratory failure subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Throat irritation subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Wheezing subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | | |
| Depression subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | | |
| Hallucination subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 4 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 17 / 58 (29.31%) 31 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 17 / 58 (29.31%) 30 | | |
| Bilirubin conjugated increased subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Blood alkaline phosphatase increased | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 5 | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Breath sounds abnormal | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Electrocardiogram QT interval abnormal | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Visual acuity tests abnormal | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|----------------|--|--|
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Fall | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Scratch | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Congenital, familial and genetic disorders | | | |
| Ichthyosis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Cardiomegaly | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tachycardia | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Burning sensation | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Clumsiness | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 9 / 58 (15.52%) | | |
| occurrences (all) | 15 | | |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 11 / 58 (18.97%) | | |
| occurrences (all) | 14 | | |
| Head discomfort | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 12 / 58 (20.69%) | | |
| occurrences (all) | 14 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|------------------------|--|--|
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 7 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | | |
| Peripheral motor neuropathy subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Somnolence subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 5 | | |
| Tremor subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 6 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 10 / 58 (17.24%) 18 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | | |
| Lymphopenia subjects affected / exposed occurrences (all) | 1 / 58 (1.72%) 1 | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 4 | | |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Hearing impaired subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Tinnitus | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 9 | | |
| Dry eye | | | |
| subjects affected / exposed | 7 / 58 (12.07%) | | |
| occurrences (all) | 8 | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Vision blurred | | | |
| subjects affected / exposed | 7 / 58 (12.07%) | | |
| occurrences (all) | 14 | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | | |
| occurrences (all) | 6 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Ascites | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 5 | | |
| Cheilitis | | | |

| | | | |
|----------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Constipation | | | |
| subjects affected / exposed | 16 / 58 (27.59%) | | |
| occurrences (all) | 20 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 17 / 58 (29.31%) | | |
| occurrences (all) | 37 | | |
| Dry mouth | | | |
| subjects affected / exposed | 19 / 58 (32.76%) | | |
| occurrences (all) | 23 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | | |
| occurrences (all) | 7 | | |
| Flatulence | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Frequent bowel movements | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lip disorder | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lip dry | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lip pain | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 27 / 58 (46.55%) | | |
| occurrences (all) | 46 | | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral dysaesthesia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 6 | | |
| Tongue disorder | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 23 / 58 (39.66%) | | |
| occurrences (all) | 48 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alopecia | | | |
| subjects affected / exposed | 11 / 58 (18.97%) | | |
| occurrences (all) | 11 | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Dry skin | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Erythema | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Rash | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash macular | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Scab | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Scar | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|--|--|--|
| <p>Skin fissures</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Skin mass</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Renal and urinary disorders</p> <p>Dysuria</p> <p>subjects affected / exposed</p> <p>1 / 58 (1.72%)</p> <p>occurrences (all)</p> <p>2</p> <p>Hydronephrosis</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Micturition frequency decreased</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Pollakiuria</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Proteinuria</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Urinary incontinence</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Endocrine disorders</p> <p>Hypothyroidism</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>4 / 58 (6.90%)</p> <p>occurrences (all)</p> <p>4</p> <p>Muscle twitching</p> <p>subjects affected / exposed</p> <p>0 / 58 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |

| | | | |
|---|---------------------|--|--|
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 58 (1.72%) 3 | | |
| Infections and infestations | | | |
| Candidiasis subjects affected / exposed occurrences (all) | 1 / 58 (1.72%) 1 | | |
| Cystitis subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 3 | | |
| Ear infection subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Oesophageal candidiasis subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 58 (1.72%) 1 | | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Skin infection subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | | |
| Upper respiratory tract infection | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 3 | | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 13 / 58 (22.41%) | | |
| occurrences (all) | 15 | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 4 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 6 | | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypochloraemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences (all) | 1 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 6 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 29 October 2012 | The original protocol was amended based on comments and/or requests from the FDA made during IND review. |
| 21 June 2013 | 1. Based on the preliminary pharmacokinetic results obtained in patients enrolled in Cohorts 1-3, new derazantinib dose escalation guidelines were introduced. 2. The study design was changed so that patients would participate in a single treatment period of continuous dosing instead of participating in two treatment periods. |
| 12 June 2014 | 1. A food-effect cohort was added 2. Inclusion / exclusion criteria were amended to permit patients to be enrolled in the Expanded Cohort 3. A specification was added with regard to collection of biopsies |
| 04 November 2014 | 1. The recommended phase 2 dose was defined as 300 mg QD (fasted) 2. The eligibility requirements for the Expanded Cohort were clarified based on tumor type and/or tumor genomic profile |
| 10 April 2015 | 1. The expanded tumor sub-cohorts were specified to include only patients with advanced solid tumors with FGFR genetic aberrations, including intrahepatic cholangiocarcinoma with FGFR2 gene fusion 2. The study title was changed to reflect the updated definition of tumor type and genomic profile 3. Changes were made to some inclusion and exclusion criteria 4. A clarification was added to dose delays / reduction for Grade 3-4 toxicity |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28972963>

<http://www.ncbi.nlm.nih.gov/pubmed/30420614>