# Clinical trial results:
# A phase II, open-label, multicenter study of Dabrafenib plus Trametinib in subjects with BRAF Mutation- positive melanoma that has metastasized to the brain.

**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.novfor complete trial results.**

## Summary

| | |
|---|---|
| EudraCT number | 2013-003452-21 |
| Trial protocol | ES DE IT |
| Global end of trial date | 14 February 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 February 2019 |
| First version publication date | 15 February 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 117277 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02039947 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novartis Pharmaceutical |
| Sponsor organisation address | CH-4002, Basel, Swaziland, |
| Public contact | Clinical Disclosure Office, Novartis Pharmaceutical, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharmaceutical, 41 613241111, |

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 | 14 February 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 14 February 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the intracranial response (IR) of subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local therapy and ECOG score of 0 or 1 (cohort A).
IR was defined as the proportion of subjects with a confirmed intracranial complete response (CR) or partial response (PR) by investigator assessment using modified RECIST 1.1 guidelines

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 | 21 February 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Canada: 11 |
| Country: Number of subjects enrolled | France: 55 |
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | Italy: 14 |
| Country: Number of subjects enrolled | Spain: 22 |
| Country: Number of subjects enrolled | United States: 12 |
| Worldwide total number of subjects | 125 |
| EEA total number of subjects | 97 |

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) | 97 |
| From 65 to 84 years | 28 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A subject was considered to have completed the study if the subject died during the study treatment or follow-up period or (for subject in Cohort A) had at least 3 years follow-up from the date of first dose of study treatment at the end of the study.

All subjects achieved that definition and then the study ended.

### 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** | Cohort A |

Arm description:

Subjects will receive dabrafenib 150 milligram (mg) twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity.

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

Dosage and administration details:

Dabrafenib- 50 mg and 75 mg capsules
Trametinib- 0.5 mg and 2.0 mg tablets

| | |
|---|---|
| Investigational medicinal product name | Dabrafenib Trametinib |
| Investigational medicinal product code | |
| Other name | Dabrafenib Trametinib |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Dabrafenib- 50 mg and 75 mg capsules
Trametinib- 0.5 mg and 2.0 mg tablets

| | |
|---|---|
| **Arm title** | Cohort B |

Arm description:

Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity

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

Dosage and administration details:

Dabrafenib- 50 mg and 75 mg capsules

| **Arm title** | Cohort C |
|---|---|
| Arm description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |
| Arm type | Experimental |
| Investigational medicinal product name | Dabrafenib Trametinibets |
| Investigational medicinal product code | |
| Other name | Dabrafenib Trametinibets |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dabrafenib- 50 mg and 75 mg capsules<br>Trametinib- 0.5 mg and 2.0 mg tablets | |

| **Arm title** | Cohort D |
|---|---|
| Arm description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |
| Arm type | Experimental |
| Investigational medicinal product name | Dabrafenib Trametinib |
| Investigational medicinal product code | |
| Other name | Dabrafenib Trametinib |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dabrafenib-50 mg and 75 mg capsules<br>Trametinib-0.5 mg and 2.0 mg tablets | |

| **Number of subjects in period 1** | Cohort A | Cohort B | Cohort C |
|---|---|---|---|
| Started | 76 | 16 | 16 |
| Completed | 76 | 16 | 16 |

| **Number of subjects in period 1** | Cohort D |
|---|---|
| Started | 17 |
| Completed | 17 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort A |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 milligram (mg) twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity. | |
| Reporting group title | Cohort B |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |
| Reporting group title | Cohort C |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |
| Reporting group title | Cohort D |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |

| Reporting group values | Cohort A | Cohort B | Cohort C |
|---|---|---|---|
| Number of subjects | 76 | 16 | 16 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 60 | 12 | 9 |
| From 65-84 years | 16 | 4 | 7 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| median | 53.2 | 55.1 | 65.6 |
| standard deviation | ± 14.69 | ± 11.05 | ± 10.40 |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 36 | 6 | 5 |
| Male | 40 | 10 | 11 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 76 | 16 | 16 |

| | | | |
|---|---|---|---|
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |

| **Reporting group values** | Cohort D | Total | |
|---|---|---|---|
| Number of subjects | 17 | 125 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 16 | 97 | |
| From 65-84 years | 1 | 28 | |
| 85 years and over | 0 | 0 | |
| Age Continuous<br>Units: Years | | | |
| median | 47.5 | | |
| standard deviation | ± 13.01 | - | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 6 | 53 | |
| Male | 11 | 72 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 0 | |
| White | 17 | 125 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort A |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 milligram (mg) twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity. | |
| Reporting group title | Cohort B |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |
| Reporting group title | Cohort C |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |
| Reporting group title | Cohort D |
| Reporting group description: | |
| Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity | |
| Subject analysis set title | All treated population |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All subjects who receive at least one dose of study medication are comprised the All Treated subjects (ATS) population. | |

### Primary: Intracranial response (IR) rate

| | |
|---|---|
| End point title | Intracranial response (IR) rate[1][2] |
| End point description: | |
| The intracranial response rate is defined as the percentage of subjects achieving a confirmed intracranial CR or PR. This is based on investigator-assessed best intracranial response. | |
| End point type | Primary |
| End point timeframe: | |
| From the start of treatment until disease progression or the start of new anti-cancer therapy | |

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: "because only Cohort A is considered for primary efficacy analysis"

[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 hypothesis testing completed for cohort B,C and D

| End point values | Cohort A | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 76 | | | |
| Units: Number of participants | 45 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Intracranial response rate of cohorts B, C and D

| End point title | Intracranial response rate of cohorts B, C and D[3] |
|---|---|

End point description:

The intracranial response rate is defined as the percentage of subjects achieving a confirmed intracranial CR or PR. This is based on investigator-assessed best intracranial response. No hypothesis testing completed for cohort B,C and D

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

End point timeframe:

Approximately 2 years

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 hypothesis testing completed for cohort B,C and D

| End point values | Cohort B | Cohort C | Cohort D | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 16 | 17 | |
| Units: Number of participants | 9 | 7 | 10 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Disease Control for intracranial, extracranial and overall response for each cohort

| End point title | Disease Control for intracranial, extracranial and overall response for each cohort |
|---|---|

End point description:

Disease Control rate is defined as the percentage of subjects achieving a confirmed intracranial/extracranial/overall CR or PR or SD or Non-CR/Non-PD. This is based on investigator-assessed response. No hypothesis testing completed for cohort B,C and D

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

End point timeframe:

Approximately 2 years

| End point values | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 16 | 16 | 17 |
| Units: Number of participants | | | | |
| Intracranial Response | 59 | 14 | 12 | 15 |
| Extracranial Response | 60 | 11 | 15 | 11 |
| Overall Response | 60 | 14 | 12 | 15 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Extracranial response rate (ER) for each cohort

| End point title | Extracranial response rate (ER) for each cohort |
|---|---|

End point description:

Disease Control rate is defined as the percentage of subjects achieving a confirmed intracranial/extracranial/overall CR or PR or SD or Non-CR/Non-PD. This is based on investigator-assessed response. No hypothesis testing completed for cohort B,C and D

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

End point timeframe:

Approximately 2 years

| End point values | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 16 | 16 | 17 |
| Units: Number of participants | 42 | 7 | 12 | 7 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall response (OR) for each cohort

| End point title | Overall response (OR) for each cohort |
|---|---|

End point description:

Disease Control rate is defined as the percentage of subjects achieving a confirmed intracranial/extracranial/overall CR or PR or SD or Non-CR/Non-PD. This is based on investigator-assessed response. No hypothesis testing completed for cohort B,C and D

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

End point timeframe:

Approximately 2 years

| End point values | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 16 | 16 | 17 |
| Units: Number of participants | 45 | 9 | 7 | 11 |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of intracranial, extracranial and overall response for each cohort

| End point title | Duration of intracranial, extracranial and overall response for each cohort |
|---|---|

End point description:

Duration of intracranial, extracranial and overall response, are defined as the time from first documented evidence of CR or PR until time of first documented intracranial, extracranial, or overall disease progression. No hypothesis testing completed for cohort B,C and D

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

End point timeframe:

From first documented evidence of CR or PR until time of first documented intracranial, extracranial, or overall disease progression

| End point values | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 16 | 16 | 17 |
| Units: Month | | | | |
| median (confidence interval 95%) | | | | |
| Duration of intracranial | 6.5 (4.9 to 8.6) | 7.3 (3.6 to 12.6) | 8.3 (1.3 to 15.0) | 4.5 (2.8 to 5.9) |
| Duration of extracranial | 10.2 (5.8 to 9999) | 9999 (9999 to 9999) | 4.9 (3.0 to 22.4) | 5.9 (1.8 to 9999) |
| Duration of Overall Response | 6.2 (4.9 to 8.3) | 12.5 (5.3 to 9999) | 6.6 (1.3 to 16.3) | 4.5 (2.8 to 11.2) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS) for each cohort Based on investigator assessment

| End point title | Progression-free survival (PFS) for each cohort Based on investigator assessment |
|---|---|

End point description:

PFS is defined as the interval between first dose and the earliest date of disease progression or death due to any cause. No hypothesis testing completed for cohort B,C and D

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

End point timeframe:

From the first dose to the earliest date of disease progression or death

| **End point values** | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 16 | 16 | 17 |
| Units: Month | | | | |
| median (confidence interval 95%) | 5.7 (5.3 to 7.3) | 7.2 (4.7 to 14.6) | 3.7 (1.7 to 6.5) | 5.5 (3.7 to 11.6) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival (OS) for each cohort

| End point title | Overall survival (OS) for each cohort |
|---|---|

End point description:

Overall survival (OS) is defined as the time from the first dose until death due to any cause. No hypothesis testing completed for cohort B,C and D

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

End point timeframe:

From the first dose to death

| **End point values** | Cohort A | Cohort B | Cohort C | Cohort D |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 16 | 16 | 17 |
| Units: Month | | | | |
| median (confidence interval 95%) | 10.8 (8.7 to 17.9) | 24.3 (7.9 to 9999) | 10.1 (4.6 to 17.6) | 11.5 (6.8 to 22.4) |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

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 | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort A |
| Reporting group description: | |
| Cohort A | |
| Reporting group title | Cohort B |
| Reporting group description: | |
| Cohort B | |
| Reporting group title | Cohort C |
| Reporting group description: | |
| Cohort C | |
| Reporting group title | Cohort D |
| Reporting group description: | |
| Cohort D | |
| Reporting group title | Total |
| Reporting group description: | |
| Total | |

| Serious adverse events | Cohort A | Cohort B | Cohort C |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 26 / 76 (34.21%) | 5 / 16 (31.25%) | 4 / 16 (25.00%) |
| number of deaths (all causes) | 54 | 10 | 15 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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 |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| 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 / 76 (0.00%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 16 (6.25%) | 2 / 16 (12.50%) |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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 |
| Troponin T increased | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachyarrhythmia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (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 | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Detachment of retinal pigment epithelium | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular detachment | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (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 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (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 | | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (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 | | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort D | Total | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 17 (52.94%) | 44 / 125 (35.20%) | |
| number of deaths (all causes) | 13 | 92 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 9 / 125 (7.20%) | |
| occurrences causally related to treatment / all | 2 / 2 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 5 / 125 (4.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Troponin T increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Detachment of retinal pigment epithelium | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular detachment | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| 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 | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Cohort A | Cohort B | Cohort C |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 74 / 76 (97.37%) | 16 / 16 (100.00%) | 16 / 16 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 2 / 16 (12.50%) |
| occurrences (all) | 0 | 1 | 2 |
| Lipoma | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Papilloma | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seborrhoeic keratosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 1 | 1 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all) | 1 | 0 | 2 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 3 / 16 (18.75%) | 3 / 16 (18.75%) |
| occurrences (all) | 6 | 3 | 4 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Peripheral venous disease | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 28 / 76 (36.84%) | 5 / 16 (31.25%) | 3 / 16 (18.75%) |
| occurrences (all) | 33 | 6 | 5 |
| Chest pain | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 5 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 18 / 76 (23.68%) | 6 / 16 (37.50%) | 7 / 16 (43.75%) |
| occurrences (all) | 33 | 13 | 8 |
| Face oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 4 / 16 (25.00%) | 8 / 16 (50.00%) |
| occurrences (all) | 7 | 5 | 9 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Ill-defined disorder | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all) | 5 | 3 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 11 / 76 (14.47%) | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all) | 14 | 2 | 4 |
| Pain | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 45 / 76 (59.21%) | 7 / 16 (43.75%) | 8 / 16 (50.00%) |
| occurrences (all) | 133 | 13 | 19 |
| Temperature regulation disorder | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Thirst | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Xerosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Prostatomegaly | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 10 / 76 (13.16%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all) | 12 | 2 | 1 |
| Dry throat | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 3 / 16 (18.75%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 3 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis allergic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Affective disorder | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Agitation | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Apathy | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Delirium | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 76 (11.84%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all) | 9 | 7 | 1 |
| Amylase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 12 / 76 (15.79%) | 3 / 16 (18.75%) | 2 / 16 (12.50%) |
| occurrences (all) | 13 | 3 | 2 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 1 / 16 (6.25%) | 2 / 16 (12.50%) |
| occurrences (all) | 6 | 1 | 2 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 3 / 16 (18.75%) | 0 / 16 (0.00%) |
| occurrences (all) | 11 | 4 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 6 | 1 | 1 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood sodium increased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 6 | 1 | 1 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 7 | 1 | 1 |
| Lipase increased | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 6 | 0 | 1 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 2 / 16 (12.50%) | 3 / 16 (18.75%) |
| occurrences (all) | 4 | 2 | 4 |
| Weight increased | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Animal bite | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Contusion | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle strain | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Aphasia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aphonia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cerebellar syndrome | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 76 (6.58%) | 5 / 16 (31.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 7 | 7 | 0 |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 1 | 1 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 28 / 76 (36.84%) | 5 / 16 (31.25%) | 6 / 16 (37.50%) |
| occurrences (all) | 47 | 9 | 9 |
| Hemianopia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Paresis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Presyncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Seizure | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 3 / 16 (18.75%) |
| occurrences (all) | 4 | 1 | 3 |
| Syncope | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 | 1 |
| Temporal lobe epilepsy | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tongue paralysis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tonic clonic movements | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 0 | 2 |
| Visual field defect | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 11 / 76 (14.47%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all) | 12 | 2 | 1 |

| | | | |
|---|---|---|---|
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 4 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Vertigo | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 0 | 1 |
| Eye disorders | | | |
| Asthenopia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Cataract | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Conjunctival irritation | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Dry eye | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Posterior capsule opacification | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Punctate keratitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Retinopathy | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Vision blurred | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 1 | 1 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vitreous detachment | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitreous floaters | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 11 | 1 | 0 |

| | | | |
|---|---|---|---|
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 1 / 16 (6.25%) | 4 / 16 (25.00%) |
| occurrences (all) | 9 | 1 | 4 |
| Diarrhoea | | | |
| subjects affected / exposed | 24 / 76 (31.58%) | 8 / 16 (50.00%) | 3 / 16 (18.75%) |
| occurrences (all) | 30 | 15 | 4 |
| Dry mouth | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all) | 5 | 2 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all) | 5 | 2 | 1 |
| Faecalith | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Faeces soft | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 24 / 76 (31.58%) | 7 / 16 (43.75%) | 4 / 16 (25.00%) |
| occurrences (all) | 42 | 9 | 5 |

| | | | |
|---|---|---|---|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Retching | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 1 / 16 (6.25%) | 2 / 16 (12.50%) |
| occurrences (all) | 3 | 1 | 3 |
| Tongue discolouration | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 24 / 76 (31.58%) | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all) | 32 | 3 | 2 |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 5 | 0 | 1 |
| Actinic elastosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Actinic keratosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 3 | 1 |
| Alopecia | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 7 | 0 | 1 |
| Aquagenic wrinkling of palms | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 76 (3.95%) | 1 / 16 (6.25%) | 3 / 16 (18.75%) |
| occurrences (all) | 4 | 1 | 3 |
| Dry skin | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 2 / 16 (12.50%) | 3 / 16 (18.75%) |
| occurrences (all) | 9 | 2 | 3 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Eczema | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 3 |
| Erythema | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 0 / 16 (0.00%) | 4 / 16 (25.00%) |
| occurrences (all) | 7 | 0 | 5 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Generalised erythema | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 4 | 0 | 1 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 7 | 1 | 0 |
| Intertrigo | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nail disorder | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Onycholysis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Pain of skin | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Palmar erythema | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 3 / 16 (18.75%) |
| occurrences (all) | 1 | 0 | 3 |
| Palmoplantar keratoderma | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Panniculitis | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Papule | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 0 / 16 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all) | 5 | 0 | 2 |
| Pruritus generalised | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 9 / 76 (11.84%) | 7 / 16 (43.75%) | 3 / 16 (18.75%) |
| occurrences (all) | 10 | 8 | 3 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash generalised | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |

| | | | |
|---|---|---|---|
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 | 1 |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin hyperplasia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin mass | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Skin striae | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Nocturia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 | 1 |
| Urinary incontinence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 15 / 76 (19.74%) | 3 / 16 (18.75%) | 2 / 16 (12.50%) |
| occurrences (all) | 22 | 5 | 2 |
| Back pain | | | |
| subjects affected / exposed | 11 / 76 (14.47%) | 1 / 16 (6.25%) | 3 / 16 (18.75%) |
| occurrences (all) | 11 | 1 | 3 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Flank pain | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 0 / 16 (0.00%) | 4 / 16 (25.00%) |
| occurrences (all) | 9 | 0 | 4 |
| Muscular weakness | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 1 / 16 (6.25%) | 2 / 16 (12.50%) |
| occurrences (all) | 5 | 1 | 2 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 13 / 76 (17.11%) | 5 / 16 (31.25%) | 2 / 16 (12.50%) |
| occurrences (all) | 17 | 10 | 3 |
| Neck pain | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 0 | 1 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 3 / 16 (18.75%) | 3 / 16 (18.75%) |
| occurrences (all) | 13 | 3 | 5 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tendonitis | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Infections and infestations | | | |
| Angular cheilitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Lung infection | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all) | 7 | 3 | 2 |
| Onychomycosis | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 16 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all) | 4 | 0 | 2 |
| Sialoadenitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 76 (11.84%) | 4 / 16 (25.00%) | 7 / 16 (43.75%) |
| occurrences (all) | 10 | 5 | 7 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Gout | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 1 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Cohort D | Total | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 17 (100.00%) | 123 / 125 (98.40%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 1 | |
| Lipoma | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 3 | |
| Papilloma | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 0 | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 3 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Flushing | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 1 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 12 / 125 (9.60%) | |
| occurrences (all) | 0 | 14 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 125 (3.20%) | |
| occurrences (all) | 3 | 4 | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Peripheral venous disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 41 / 125 (32.80%) | |
| occurrences (all) | 7 | 58 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 4 | |
| Chills | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 37 / 125 (29.60%) | |
| occurrences (all) | 10 | 52 | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 2 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 22 / 125 (17.60%) | |
| occurrences (all) | 4 | 26 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 3 | |
| Ill-defined disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 8 / 125 (6.40%) | |
| occurrences (all) | 0 | 9 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 18 / 125 (14.40%) | |
| occurrences (all) | 3 | 23 | |
| Pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 125 (3.20%) | |
| occurrences (all) | 1 | 4 | |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| subjects affected / exposed | 8 / 17 (47.06%) | 68 / 125 (54.40%) | |
| occurrences (all) | 30 | 161 | |
| Temperature regulation disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 3 | |
| Thirst | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Xerosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 125 (3.20%) | |
| occurrences (all) | 1 | 5 | |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 2 | 2 | |
| Prostatomegaly | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 16 / 125 (12.80%) | |
| occurrences (all) | 3 | 18 | |
| Dry throat | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 6 / 125 (4.80%) | |
| occurrences (all) | 1 | 6 | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 8 / 125 (6.40%) | |
| occurrences (all) | 2 | 7 | |

| | | | |
|---|---|---|---|
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Wheezing | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Psychiatric disorders | | | |
| Affective disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Agitation | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 125 (3.20%) | |
| occurrences (all) | 1 | 4 | |
| Apathy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 2 | 4 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 8 / 125 (6.40%) | |
| occurrences (all) | 2 | 7 | |
| Depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 3 | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 15 / 125 (12.00%) | |
| occurrences (all) | 3 | 20 | |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 20 / 125 (16.00%) | |
| occurrences (all) | 3 | 21 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 12 / 125 (9.60%) | |
| occurrences (all) | 3 | 12 | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 2 | 2 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 10 / 125 (8.00%) | |
| occurrences (all) | 0 | 17 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 8 / 125 (6.40%) | |
| occurrences (all) | 0 | 8 | |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Blood potassium decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 0 | |
| Blood sodium increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 5 / 125 (4.00%) | |
| occurrences (all) | 0 | 6 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 7 / 125 (5.60%) | |
| occurrences (all) | 1 | 9 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 13 / 125 (10.40%) | |
| occurrences (all) | 4 | 17 | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 125 (3.20%) | |
| occurrences (all) | 1 | 6 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 6 / 125 (4.80%) | |
| occurrences (all) | 1 | 8 | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 3 | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 12 / 125 (9.60%) | |
| occurrences (all) | 3 | 13 | |

| | | | |
|---|---|---|---|
| Weight increased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 6 / 125 (4.80%) | |
| occurrences (all) | 2 | 6 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 3 | |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Fall | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac disorders | | | |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Aphasia | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 4 / 125 (3.20%) | |
| occurrences (all) | 3 | 4 | |

| | | | |
|---|---|---|---|
| Aphonia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Cerebellar syndrome | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 13 / 125 (10.40%) | |
| occurrences (all) | 3 | 14 | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 4 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Headache | | | |
| subjects affected / exposed | 8 / 17 (47.06%) | 47 / 125 (37.60%) | |
| occurrences (all) | 13 | 70 | |
| Hemianopia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Motor dysfunction | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 8 / 125 (6.40%) | |
| occurrences (all) | 2 | 8 | |
| Paresis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Partial seizures | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 125 (1.60%) | |
| occurrences (all) | 2 | 1 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 1 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Seizure | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 9 / 125 (7.20%) | |
| occurrences (all) | 3 | 6 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 0 | |
| Temporal lobe epilepsy | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Tongue paralysis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Tonic clonic movements | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 5 | |
| Visual field defect | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 17 (11.76%) | 6 / 125 (4.80%) | |
| occurrences (all) | 2 | 10 | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 4 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 14 / 125 (11.20%) | |
| occurrences (all) | 0 | 18 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 7 / 125 (5.60%) | |
| occurrences (all) | 2 | 7 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 3 | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 3 | |
| Eye disorders | | | |
| Asthenopia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Cataract | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Conjunctival irritation | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Dry eye | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | | |
| occurrences (all) | 1 | 3 | | |
| Eye pain | | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | | |
| occurrences (all) | 0 | 1 | | |
| Eye pruritus | | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | | |
| occurrences (all) | 2 | 2 | | |
| Eyelid oedema | | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 3 / 125 (2.40%) | | |
| occurrences (all) | 3 | 4 | | |
| Lacrimation increased | | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | | |
| occurrences (all) | 0 | 2 | | |
| Posterior capsule opacification | | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | | |
| occurrences (all) | 0 | 1 | | |
| Punctate keratitis | | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | | |
| occurrences (all) | 1 | 1 | | |
| Retinopathy | | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | | |
| occurrences (all) | 0 | 1 | | |
| Vision blurred | | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 6 / 125 (4.80%) | | |
| occurrences (all) | 1 | 5 | | |
| Visual acuity reduced | | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | | |
| occurrences (all) | 1 | 1 | | |
| Visual impairment | | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 3 / 125 (2.40%) | | |
| occurrences (all) | 2 | 2 | | |
| Vitreous detachment | | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | | |
| occurrences (all) | 1 | 1 | | |
| Vitreous floaters | | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 4 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 14 / 125 (11.20%) | |
| occurrences (all) | 8 | 18 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 7 / 125 (5.60%) | |
| occurrences (all) | 4 | 10 | |
| Constipation | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 19 / 125 (15.20%) | |
| occurrences (all) | 9 | 23 | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 17 (41.18%) | 42 / 125 (33.60%) | |
| occurrences (all) | 11 | 54 | |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 11 / 125 (8.80%) | |
| occurrences (all) | 3 | 12 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 8 / 125 (6.40%) | |
| occurrences (all) | 0 | 8 | |
| Faecalith | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Faeces soft | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 3 | |
| Nausea | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 41 / 125 (32.80%) | |
| occurrences (all) | 9 | 49 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 5 | |
| Retching | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 6 / 125 (4.80%) | |
| occurrences (all) | 0 | 7 | |
| Tongue discolouration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 34 / 125 (27.20%) | |
| occurrences (all) | 10 | 32 | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 6 / 125 (4.80%) | |
| occurrences (all) | 0 | 6 | |
| Actinic elastosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Actinic keratosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 2 | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 10 / 125 (8.00%) | |
| occurrences (all) | 2 | 10 | |
| Aquagenic wrinkling of palms | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 8 / 125 (6.40%) | |
| occurrences (all) | 1 | 9 | |
| Dry skin | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 15 / 125 (12.00%) | |
| occurrences (all) | 4 | 17 | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Eczema | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 5 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 10 / 125 (8.00%) | |
| occurrences (all) | 2 | 14 | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Generalised erythema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 6 / 125 (4.80%) | |
| occurrences (all) | 1 | 6 | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 8 / 125 (6.40%) | |
| occurrences (all) | 0 | 6 | |
| Intertrigo | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 125 (4.00%) | |
| occurrences (all) | 1 | 5 | |
| Nail disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 1 | |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Pain of skin | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Palmar erythema | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 4 | |
| Palmoplantar keratoderma | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Panniculitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 4 | |
| Papule | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 9 / 125 (7.20%) | |
| occurrences (all) | 2 | 8 | |
| Pruritus generalised | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |

| | | | |
|---|---|---|---|
| Rash | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 22 / 125 (17.60%) | |
| occurrences (all) | 4 | 26 | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 5 / 125 (4.00%) | |
| occurrences (all) | 0 | 5 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Skin exfoliation | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Skin hyperplasia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 2 | 4 | |
| Skin mass | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Skin striae | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 3 | |
| Nocturia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 26 / 125 (20.80%) | |
| occurrences (all) | 11 | 39 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 17 / 125 (13.60%) | |
| occurrences (all) | 3 | 15 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 1 | |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 12 / 125 (9.60%) | |
| occurrences (all) | 1 | 13 | |
| Muscular weakness | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 9 / 125 (7.20%) | |
| occurrences (all) | 5 | 12 | |
| Musculoskeletal chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 125 (4.00%) | |
| occurrences (all) | 1 | 5 | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Myalgia | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 26 / 125 (20.80%) | |
| occurrences (all) | 7 | 39 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 125 (4.00%) | |
| occurrences (all) | 1 | 5 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 16 / 125 (12.80%) | |
| occurrences (all) | 2 | 23 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Infections and infestations | | | |
| Angular cheilitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 125 (4.00%) | |
| occurrences (all) | 2 | 6 | |

| | | | |
|---|---|---|---|
| Cellulitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Folliculitis | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 10 / 125 (8.00%) | |
| occurrences (all) | 4 | 10 | |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 7 / 125 (5.60%) | |
| occurrences (all) | 0 | 8 | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 11 / 125 (8.80%) | |
| occurrences (all) | 0 | 11 | |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 125 (3.20%) | |
| occurrences (all) | 1 | 4 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 125 (3.20%) | |
| occurrences (all) | 0 | 6 | |

| | | | |
|---|---|---|---|
| Paronychia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 3 | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 2 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 6 / 125 (4.80%) | |
| occurrences (all) | 0 | 6 | |
| Sialoadenitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 125 (0.80%) | |
| occurrences (all) | 1 | 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 125 (2.40%) | |
| occurrences (all) | 0 | 2 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 6 / 125 (4.80%) | |
| occurrences (all) | 2 | 6 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 23 / 125 (18.40%) | |
| occurrences (all) | 3 | 28 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 125 (1.60%) | |
| occurrences (all) | 1 | 2 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Gout | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 125 (1.60%) | |
| occurrences (all) | 0 | 2 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 5 / 125 (4.00%) | |
| occurrences (all) | 2 | 5 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 3 / 125 (2.40%) | |
| occurrences (all) | 4 | 5 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 125 (2.40%) | |
| occurrences (all) | 1 | 3 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 125 (4.00%) | |
| occurrences (all) | 2 | 6 | |
| Hypophosphataemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 2 / 17 (11.76%)<br>2 | 2 / 125 (1.60%)<br>2 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 27 April 2014 | • Survival follow-up period has been extended in order to collect additional long-term overall survival data.<br>• Addition of secondary objective of long-term (particularly 5-year) OS.<br>• Additional information available: Dabrafenib, another small molecule BRAF-inhibitor received FDA-approval in May 2013 and<br>EMA approval in August 2013.<br>• Reference to abstaining to any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos was<br>removed.<br>• Additional information available: In Jan-2014 the combination of dabrafenib and trametinib received FDA approval, and in<br>February 2014 the combination received approval in Australia. |
| 20 August 2014 | A country-specific amendment as requested by the French regulatory agency |
| 16 March 2015 | •Study design revised for clarity around treatment discontinuation and follow up of subjects.<br>• Exclusion HIV removed per March 2014 updates to Inc/Exc (combination).<br>• Permanent discontinuation from study treatment revised for clarity around treatment discontinuation and follow up of subjects.<br>• Dosage and administration section revised based on combination dosage and administration March 2014 |
| 06 December 2015 | • Study Objectives: 1. Primary endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation<br>as with all other cohorts) and 2. Secondary endpoint number 9 OS changed from 5 to 3 year.<br>• Cohort A subject population updated to allow for locally confirmed BRAF V600E (followed by central confirmation as with all<br>other cohorts). And definition of study closure updated from "where all subjects still in follow up have had at least 5 years follow<br>up…" to "where all subjects still in follow up have had at least 3 years follow up…"<br>• Discussion of Design – primary efficacy objective endpoint amended to allow for locally confirmed BRAF V600E (followed by<br>central confirmation as with all other cohorts) |
| 13 July 2016 | •Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents.<br>• Make administrative changes to align with Novartis processes and procedures |
| 16 May 2017 | Amendment 6 did not incorporate amendment 5, as it was only for submission in countries that had not submitted GSK<br>to Novartis sponsorship change<br>• Study design section amended to define study close as when 70% of Cohort A subjects are lost to follow up or completed or<br>when all Cohort A subjects have been followed up for 3 years, whichever is earlier.<br>• Section 10.5 – Study closure definition amended from 70% of all enrolled study population to 70% of primary efficacy<br>population (Cohort A) and addition of at least three years follow up for all Cohort A subjects Estimation |

| | |
|---|---|
| 21 June 2017 | Amendment 7 did incorporate amendment 5, as it was for submission in countries that had already submitted GSK to<br>Novartis sponsorship change<br>● Study design section amended to define study close as when 70% of Cohort A subjects are lost to follow up or completed or<br>when all Cohort A subjects have been followed up for 3 years, whichever is earlier.<br>● Section 10.5 – Study closure definition amended from 70% of all enrolled study population to 70% of primary efficacy<br>population (Cohort A) and addition of at least three years follow up for all Cohort A subjects. Estimation of study length amended<br>to approximately 5 years from study start |

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.novfor complete trial results. |

Notes: