# Clinical trial results:
# A Phase I/II, Multicenter, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of Cobimetinib In Pediatric and Young Adult Patients with Previously Treated Solid Tumors

## Summary

| | |
|---|---|
| EudraCT number | 2014-004685-25 |
| Trial protocol | NL IE DK GB DE ES IT FR |
| Global end of trial date | 21 July 2021 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 24 March 2022 |
| First version publication date | 05 February 2022 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | GO29665 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02639546 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-001425-PIP01-13 |
| 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 | 21 July 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 21 July 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the Safety and Pharmacokinetics of Cobimetinib

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 May 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Israel: 7 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | United States: 14 |
| Worldwide total number of subjects | 56 |
| EEA total number of subjects | 25 |

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) | 41 |

| | |
|---|---|
| Adolescents (12-17 years) | 14 |
| Adults (18-64 years) | 1 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 17 centers in 7 countries.

### Pre-assignment

Screening details:

A total of 63 participants were screened, of which a total of 56 participants were enrolled. Tumor type was not a determinant of cohort assignment for the phase I portion of the study. The phase II portion of the study was restricted to participants with Low-Grade Glioma.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Phase I (Tablet) Cobimetinib (0.6 mg/kg) |

Arm description:

Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

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

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 0.6 mg/kg.

| | |
|---|---|
| **Arm title** | Phase I (Tablet) Cobimetinib (0.8 mg/kg) |

Arm description:

Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

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

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 0.8 mg/kg.

| | |
|---|---|
| **Arm title** | Phase I (Tablet) Cobimetinib (1 mg/kg) |

Arm description:

Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

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

| | |
|---|---|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 1 mg/kg.

| | |
|---|---|
| **Arm title** | Phase I (Suspension) Cobimetinib (0.6 mg/kg) |

Arm description:

Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 0.6 mg/kg.

| | |
|---|---|
| **Arm title** | Phase I (Suspension) Cobimetinib (0.8 mg/kg) |

Arm description:

Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 0.8 mg/kg.

| | |
|---|---|
| **Arm title** | Phase I (Suspension) Cobimetinib (1 mg/kg) |

Arm description:

Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 1 mg/kg.

| | |
|---|---|
| **Arm title** | Phase I (Suspension) Cobimetinib (1.33 mg/kg) |

Arm description:

Dose-Escalation: Participants received 1.33 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

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

| | |
|---|---|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 1.33 mg/kg.

| **Arm title** | Phase II (Suspension) Cobimetinib (1 mg/kg) |
|---|---|

Arm description:

Dose-Expansion: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally once daily at a dose of 1 mg/kg.

| **Number of subjects in period 1** | Phase I (Tablet) Cobimetinib (0.6 mg/kg) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) | Phase I (Tablet) Cobimetinib (1 mg/kg) |
|---|---|---|---|
| Started | 6 | 6 | 6 |
| Completed | 0 | 0 | 0 |
| Not completed | 6 | 6 | 6 |
| Withdrawal By Subject | 2 | 2 | 1 |
| Study Terminated By Sponsor | - | 2 | 3 |
| Death | 2 | 2 | 1 |
| Lost to follow-up | - | - | 1 |
| PI, physician decision; no response to trt. | 2 | - | - |

| **Number of subjects in period 1** | Phase I (Suspension) Cobimetinib (0.6 mg/kg) | Phase I (Suspension) Cobimetinib (0.8 mg/kg) | Phase I (Suspension) Cobimetinib (1 mg/kg) |
|---|---|---|---|
| Started | 6 | 7 | 8 |
| Completed | 0 | 0 | 0 |
| Not completed | 6 | 7 | 8 |
| Withdrawal By Subject | - | - | 1 |
| Study Terminated By Sponsor | 4 | 4 | 3 |
| Death | 2 | 2 | 2 |
| Lost to follow-up | - | 1 | 1 |
| PI, physician decision; no response to trt. | - | - | 1 |

| **Number of subjects in period 1** | Phase I (Suspension) | Phase II (Suspension) |
|---|---|---|

| | Cobimetinib (1.33 mg/kg) | Cobimetinib (1 mg/kg) |
|---|---|---|
| Started | 5 | 12 |
| Completed | 0 | 0 |
| Not completed | 5 | 12 |
| Withdrawal By Subject | 2 | 1 |
| Study Terminated By Sponsor | 3 | 9 |
| Death | - | - |
| Lost to follow-up | - | 1 |
| PI, physician decision; no response to trt. | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Phase I (Tablet) Cobimetinib (0.6 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Tablet) Cobimetinib (0.8 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Tablet) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (0.6 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (0.8 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (1.33 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1.33 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase II (Suspension) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Expansion: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |

| Reporting group values | Phase I (Tablet) Cobimetinib (0.6 mg/kg) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) | Phase I (Tablet) Cobimetinib (1 mg/kg) |
|---|---|---|---|
| Number of subjects | 6 | 6 | 6 |
| 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) | 3 | 4 | 5 |
| Adolescents (12-17 years) | 3 | 2 | 1 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 11.8 | 9.5 | 9.5 |
| standard deviation | ± 3.5 | ± 3.3 | ± 3.4 |
| Sex: Female, Male<br>Units: | | | |
| Female | 1 | 2 | 4 |
| Male | 5 | 4 | 2 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | 0 |
| Not Hispanic or Latino | 5 | 3 | 4 |
| Not Stated | 0 | 2 | 2 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Asian | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 1 |
| Unknown | 1 | 1 | 2 |
| White | 5 | 4 | 3 |
| Tumor Type<br>Units: Subjects | | | |
| Neuroblastoma | 0 | 0 | 1 |
| High-Grade Glioma | 3 | 1 | 0 |
| Low-Grade Glioma | 1 | 2 | 4 |
| Dnet In Noonan's Syndrome | 0 | 0 | 0 |
| Malignant Peripheral Nerve Sheath Tumor | 0 | 0 | 0 |
| Metastatic Mediastinal Yolksac Tumor | 1 | 0 | 0 |
| Non-Rhabdomyosarcoma Soft Tissue Sarcoma | 0 | 1 | 0 |
| Plexiform Neurofibroma | 1 | 2 | 1 |
| Rhabdoid Tumor/ATRT | 0 | 0 | 0 |

| **Reporting group values** | Phase I (Suspension) Cobimetinib (0.6 mg/kg) | Phase I (Suspension) Cobimetinib (0.8 mg/kg) | Phase I (Suspension) Cobimetinib (1 mg/kg) |
|---|---|---|---|
| Number of subjects | 6 | 7 | 8 |
| 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) | 6 | 5 | 6 |
| Adolescents (12-17 years) | 0 | 2 | 2 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 8.5 | 9.7 | 8.9 |
| standard deviation | ± 1.4 | ± 5.3 | ± 3.1 |
| Sex: Female, Male<br>Units: | | | |
| Female | 2 | 0 | 2 |
| Male | 4 | 7 | 6 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 2 | 1 |
| Not Hispanic or Latino | 1 | 2 | 4 |
| Not Stated | 4 | 3 | 3 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Asian | 0 | 1 | 0 |
| Black or African American | 1 | 0 | 0 |
| Unknown | 5 | 4 | 3 |
| White | 0 | 2 | 5 |
| Tumor Type<br>Units: Subjects | | | |
| Neuroblastoma | 0 | 0 | 0 |
| High-Grade Glioma | 0 | 1 | 0 |
| Low-Grade Glioma | 5 | 3 | 2 |
| Dnet In Noonan's Syndrome | 0 | 0 | 0 |
| Malignant Peripheral Nerve Sheath Tumor | 0 | 1 | 1 |
| Metastatic Mediastinal Yolksac Tumor | 0 | 0 | 0 |
| Non-Rhabdomyosarcoma Soft Tissue Sarcoma | 0 | 0 | 0 |
| Plexiform Neurofibroma | 1 | 2 | 4 |
| Rhabdoid Tumor/ATRT | 0 | 0 | 1 |

| **Reporting group values** | Phase I (Suspension) Cobimetinib (1.33 mg/kg) | Phase II (Suspension) Cobimetinib (1 mg/kg) | Total |
|---|---|---|---|
| Number of subjects | 5 | 12 | 56 |
| 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) | 3 | 9 | 41 |
| Adolescents (12-17 years) | 2 | 2 | 14 |
| Adults (18-64 years) | 0 | 1 | 1 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 10.2 | 8.7 | |
| standard deviation | ± 3.3 | ± 7.5 | - |
| Sex: Female, Male<br>Units: | | | |
| Female | 5 | 7 | 23 |
| Male | 0 | 5 | 33 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 4 | 11 |
| Not Hispanic or Latino | 3 | 7 | 29 |
| Not Stated | 1 | 1 | 16 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Asian | 0 | 0 | 1 |
| Black or African American | 0 | 0 | 3 |
| Unknown | 1 | 1 | 18 |
| White | 4 | 11 | 34 |
| Tumor Type<br>Units: Subjects | | | |
| Neuroblastoma | 0 | 0 | 1 |
| High-Grade Glioma | 0 | 0 | 5 |
| Low-Grade Glioma | 3 | 12 | 32 |
| Dnet In Noonan's Syndrome | 1 | 0 | 1 |
| Malignant Peripheral Nerve Sheath Tumor | 0 | 0 | 2 |
| Metastatic Mediastinal Yolksac Tumor | 0 | 0 | 1 |
| Non-Rhabdomyosarcoma Soft Tissue Sarcoma | 0 | 0 | 1 |
| Plexiform Neurofibroma | 1 | 0 | 12 |
| Rhabdoid Tumor/ATRT | 0 | 0 | 1 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Phase I (Tablet) Cobimetinib (0.6 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Tablet) Cobimetinib (0.8 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Tablet) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (0.6 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (0.8 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (1.33 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1.33 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase II (Suspension) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Expansion: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Subject analysis set title | Cobimetinib (Tablet) Population |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received Cobimetinib (Tablet) Formulation. | |
| Subject analysis set title | Cobimetinib (Suspension) Population |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received Cobimetinib (Suspension) Formulation. | |
| Subject analysis set title | Neuroblastoma |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants with Neuroblastoma. | |
| Subject analysis set title | High Grade Glioma |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants with High Grade Glioma. | |
| Subject analysis set title | Low Grade Glioma (Phase I and II) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Low Grade Glioma.

| Subject analysis set title | Dnet In Noonan's Syn Tumr (RAS/RAF/MEK/ERK Pathway Activation) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Dnet In Noonan's Syndrome Tumor With RAS/RAF/MEK/ERK Pathway Activation.

| Subject analysis set title | Malignant Peripheral Nerve Sheath Tumor |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Malignant Peripheral Nerve Sheath Tumor.

| Subject analysis set title | Metstic Mdstnl Ylksc Tumr (RAS/RAF/MEK/ERK Pathway Activation) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Metastatic Mediastinal Yolksac Tumor With RAS/RAF/MEK/ERK Pathway Activation.

| Subject analysis set title | Non-Rhabdomyosarcoma Soft Tissue Sarcoma |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Non-Rhabdomyosarcoma Soft Tissue Sarcoma.

| Subject analysis set title | Plexiform Neurofibroma |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Plexiform Neurofibroma.

| Subject analysis set title | Rhabdoid Tumor/ATRT |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Rhabdoid Tumor/ATRT.

| Subject analysis set title | Low Grade Glioma (Phase II) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants with Low Grade Glioma.

| Subject analysis set title | Phase I (Tablet) Cobimetinib (0.6 mg/kg) (PK Population) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| Subject analysis set title | Phase I (Tablet) Cobimetinib (0.8 mg/kg) (PK Population) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| Subject analysis set title | Phase I (Tablet) Cobimetinib (1 mg/kg) (PK Population) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| Subject analysis set title | Phase I (Suspension) Cobimetinib (0.6 mg/kg) (PK Population) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| Subject analysis set title | Phase I (Suspension) Cobimetinib (0.8 mg/kg) (PK Population) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| | |
|---|---|
| Subject analysis set title | Phase I (Suspension) Cobimetinib (1 mg/kg) (PK Population) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| | |
|---|---|
| Subject analysis set title | Phase I (Suspension) Cobimetinib (1.33 mg/kg) (PK Population) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Escalation: Participants received 1.33 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

| | |
|---|---|
| Subject analysis set title | Phase II (Suspension) Cobimetinib (1 mg/kg) (PK Population) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Dose-Expansion: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle.

## Primary: Percentage of Participants with Dose-Limiting Toxicities (DLTs)

| | |
|---|---|
| End point title | Percentage of Participants with Dose-Limiting Toxicities |

End point description:

Dose-Limiting Toxicities (DLTs) were defined as cobimetinib-related adverse events occurring within the first 28 days of each administration of cobimetinib.

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

End point timeframe:

Baseline up until 30 days after the last dose of study drug (up to 5 years, 2 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| **End point values** | Phase I (Tablet) Cobimetinib (0.6 mg/kg) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) | Phase I (Tablet) Cobimetinib (1 mg/kg) | Phase I (Suspension) Cobimetinib (0.6 mg/kg) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 6 | 6 | 6 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 0 | 0 | 33.3 | 16.7 |

| **End point values** | Phase I (Suspension) Cobimetinib (0.8 mg/kg) | Phase I (Suspension) Cobimetinib (1 mg/kg) | Phase I (Suspension) Cobimetinib (1.33 mg/kg) | Phase II (Suspension) Cobimetinib (1 mg/kg) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 8 | 5 | 12 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 0 | 0 | 60.0 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants with Adverse Events (AEs), including Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)

| End point title | Percentage of Participants with Adverse Events (AEs), including Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)[2] |
|---|---|

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs.

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

End point timeframe:

Baseline up until 30 days after the last dose of study drug (up to 5 years, 2 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| End point values | Phase I (Tablet) Cobimetinib (0.6 mg/kg) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) | Phase I (Tablet) Cobimetinib (1 mg/kg) | Phase I (Suspension) Cobimetinib (0.6 mg/kg) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 6 | 6 | 6 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| AEs | 100.0 | 100.0 | 100.0 | 100.0 |
| SAEs | 33.3 | 33.3 | 33.3 | 33.3 |
| AESIs | 33.3 | 33.3 | 33.3 | 50.0 |

| End point values | Phase I (Suspension) Cobimetinib (0.8 mg/kg) | Phase I (Suspension) Cobimetinib (1 mg/kg) | Phase I (Suspension) Cobimetinib (1.33 mg/kg) | Phase II (Suspension) Cobimetinib (1 mg/kg) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 8 | 5 | 12 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| AEs | 100.0 | 100.0 | 100.0 | 100.0 |
| SAEs | 14.3 | 25.0 | 40.0 | 41.7 |

| | | | | |
|---|---|---|---|---|
| AESIs | 42.9 | 25.0 | 100.0 | 58.3 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) of Cobimetinib

| End point title | Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) of Cobimetinib[3] |
|---|---|

End point description:

A prior dose level was defined as an MTD/MAD if at a certain dose level, there were greater than or equal to (>=) 2 out of 6 participants who had Dose Limiting Toxicities (DLTs).

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

End point timeframe:

Cycle 1 Day 1 up to Cycle 1 Day 28 (cycle length=28 days)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| End point values | Cobimetinib (Tablet) Population | Cobimetinib (Suspension) Population | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 18 | 38 | | |
| Units: mg/kg | | | | |
| number (not applicable) | 0.8 | 1 | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants with Objective Response (Complete Response (CR) or Partial Response (PR)) as Determined by the Investigator using modified International Neuroblastoma Response Criteria (mINRC) for Participants with Neuroblastoma (Phase I)

| End point title | Percentage of Participants with Objective Response (Complete Response (CR) or Partial Response (PR)) as Determined by the Investigator using modified International Neuroblastoma Response Criteria (mINRC) for Participants with Neuroblastoma (Phase I)[4] |
|---|---|

End point description:

Tumor assessment was performed using mINRC for Participants with Neuroblastoma. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.

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

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (up to 5 years, 2 months)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| **End point values** | Neuroblastoma | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1 | | | |
| Units: Percentage of Participants | 0 | | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants with Objective Response (CR or PR) as Determined by the Investigator using RANO criteria for Participants with High-Grade Glioma (HGG) (Phase I) and RECIST v1.1 for Participants with Low-Grade Glioma (LGG) (Phase I and II)

| End point title | Percentage of Participants with Objective Response (CR or PR) as Determined by the Investigator using RANO criteria for Participants with High-Grade Glioma (HGG) (Phase I) and RECIST v1.1 for Participants with Low-Grade Glioma (LGG) (Phase I and II)[5] |
|---|---|

End point description:

Tumor assessment was performed using Response Assessment in Neuro-Oncology (RANO) criteria for participants with HGG and Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for participants with LGG. While the data for LGG in the phase II cohort is presented separately in other parts of the record, it was also considered useful to combine the data for LGG from phase I and phase II, which was done here. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. For phase II, only one tumor type cohort was opened (LGG). As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.

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

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (up to 5 years, 2 months)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| **End point values** | High Grade Glioma | Low Grade Glioma (Phase I and II) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 32 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 0 | 9.4 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants with Objective Response (CR or PR) as Determined by the Investigator using RECIST v1.1 criteria for Participants with All Other Tumours (Phase I)

| End point title | Percentage of Participants with Objective Response (CR or PR) as Determined by the Investigator using RECIST v1.1 criteria for Participants with All Other Tumours (Phase I)[6] |
|---|---|

End point description:

Tumor assessment was performed using RECIST v1.1 for Participants with All Other Tumours. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.

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

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (up to 5 years, 2 months)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| End point values | Dnet In Noonan's Syn Tumr (RAS/RAF/MEK /ERK Pathway Activation) | Malignant Peripheral Nerve Sheath Tumor | Metstic Mdstnl Ylksc Tumr (RAS/RAF/MEK /ERK Pathway Activation) | Non-Rhabdomyosarcoma Soft Tissue Sarcoma |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 2 | 1 | 1 |
| Units: Percentage of Participants | 0 | 0 | 0 | 0 |

| End point values | Plexiform Neurofibroma | Rhabdoid Tumor/ATRT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 1 | | |
| Units: Percentage of Participants | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants with Objective Response (CR or PR) as Determined by the Investigator using RANO criteria for Participants with LGG (Phase II)

| End point title | Percentage of Participants with Objective Response (CR or PR) as Determined by the Investigator using RANO criteria for Participants with LGG (Phase II)[7] |
|---|---|

End point description:

Tumor assessment was performed using RANO criteria for LGG. The safety evaluable population was defined as all participants who received at least one dose of study drug. For phase II, only one tumor type cohort was opened (LGG).

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

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (up to 5 years, 2 months)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| **End point values** | Low Grade Glioma (Phase II) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 12 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 8.3 | | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Progression-Free Survival (PFS) as Determined by the Investigator using mINRC for Participants with Neuroblastoma (Phase I)

| End point title | Progression-Free Survival (PFS) as Determined by the Investigator using mINRC for Participants with Neuroblastoma (Phase I)[8] |
|---|---|

End point description:

Tumor assessment was performed using mINRC for Participants with Neuroblastoma. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.
0.0 to 9999999 = The confidence interval could not be calculated from the data of one participant.

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

End point timeframe:

From the time of cobimetinib study drug initiation to the first documented disease progression, or death due to any cause, whichever occurs first (up to 5 years, 2 months)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| End point values | Neuroblastoma | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 1.3 (0.0 to 9999999) | | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: PFS as Determined by the Investigator using RANO criteria for participants with HGG (Phase I) and RECIST v1.1 for partcipants with LGG (Phase I and II)

| End point title | PFS as Determined by the Investigator using RANO criteria for participants with HGG (Phase I) and RECIST v1.1 for partcipants with LGG (Phase I and II)[9] |
|---|---|

End point description:

Tumor assessment was performed using RANO for participants with HGG and RECIST v1.1 for participants with LGG. While the data for LGG in the phase II cohort is presented separately in other parts of the record, it was also considered useful to combine the data for LGG from phase I and phase II, which was done here. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. For phase II, only one tumor type cohort was opened (LGG). As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type. 9999999 = The upper limit could not be calculated from the data due to insufficient number of participants with events.

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

End point timeframe:

From the time of cobimetinib study drug initiation to the first documented disease progression, or death due to any cause, whichever occurs first (up to approximately 6.75 years)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| End point values | High Grade Glioma | Low Grade Glioma (Phase I and II) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 32 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 1.0 (0.6 to 9999999) | 22.0 (9.3 to 9999999) | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: PFS as Determined by the Investigator using RECIST v1.1 criteria for Participants with All Other Tumours (Phase I)

| End point title | PFS as Determined by the Investigator using RECIST v1.1 |
|---|---|

| | |
|---|---|
| | criteria for Participants with All Other Tumours (Phase I)[10] |

End point description:

Tumor assessment was performed using RECIST v1.1 for Participants with All Other Tumours. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.
9999999 = The median, upper and lower limits could not be calculated from the data due to insufficient number of participants with events.

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

End point timeframe:

From the time of cobimetinib study drug initiation to the first documented disease progression, or death due to any cause, whichever occurs first (up to 5 years, 2 months)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| **End point values** | Dnet In Noonan's Syn Tumr (RAS/RAF/MEK /ERK Pathway Activation) | Malignant Peripheral Nerve Sheath Tumor | Metstic Mdstnl Ylksc Tumr (RAS/RAF/MEK /ERK Pathway Activation) | Non-Rhabdomyosarcoma Soft Tissue Sarcoma |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 2 | 1 | 1 |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (0.0 to 9999999) | 4.1 (0.7 to 9999999) | 1.1 (0.0 to 9999999) | 3.4 (0.0 to 9999999) |

| **End point values** | Plexiform Neurofibroma | Rhabdoid Tumor/ATRT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 1 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (18.4 to 9999999) | 0.5 (0.0 to 9999999) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: PFS as Determined by the Investigator using RANO criteria for Participants with LGG (Phase II)

| | |
|---|---|
| End point title | PFS as Determined by the Investigator using RANO criteria for Participants with LGG (Phase II)[11] |

End point description:

Tumor assessment was performed using RANO criteria for Participants with LGG. The safety evaluable population was defined as all participants who received at least one dose of study drug. For phase II, only one tumor type cohort was opened (LGG).
9999999 = The upper limit could not be calculated from the data due to insufficient number of participants with events.

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

End point timeframe:

From the time of cobimetinib study drug initiation to the first documented disease progression, or death due to any cause, whichever occurs first (up to 5 years, 2 months)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analyses provided as no formal hypothesis testing was planned for this study.

| **End point values** | Low Grade Glioma (Phase II) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 12 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.4 (3.6 to 9999999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Recommended Phase II Dose (RP2D) of Cobimetinib

| End point title | Recommended Phase II Dose (RP2D) of Cobimetinib |
|---|---|

End point description:

A prior dose level was defined as an RP2D if at a certain dose level, there were greater than or equal to (≥) 2 out of 6 participants who had Dose Limiting Toxicities (DLTs).

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

End point timeframe:

Cycle 1 Day 1 up to Cycle 1 Day 28 (cycle length=28 days)

| **End point values** | Cobimetinib (Suspension) Population | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: mg/kg | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR) as Determined by the Investigator using RECIST v1.1 for participants with LGG (Phase I and II)

| End point title | Duration of Response (DOR) as Determined by the Investigator using RECIST v1.1 for participants with LGG (Phase I and II) |
|---|---|

End point description:

Tumor assessment was performed using RECIST v1.1 criteria for participants with LGG. While the data for LGG in the phase II cohort is presented separately in other parts of the record, it was also considered useful to combine the data for LGG from phase I and phase II, which was done here. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. For phase II, only one tumor type cohort was opened (LGG). As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.
9999999, 0.0 to 9999999 = no participants experienced an event and DOR wasn't reached.

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

End point timeframe:

From first occurrence of objective response to disease progression or death due to any cause, whichever occurs first (up to 5 years, 2 months)

| **End point values** | Low Grade Glioma (Phase I and II) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (0.0 to 9999999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: DOR as Determined by the Investigator RANO criteria for Participants with LGG (Phase II)

| End point title | DOR as Determined by the Investigator RANO criteria for Participants with LGG (Phase II) |
|---|---|

End point description:

Tumor assessment was performed using RANO criteria for Participants with LGG. The safety evaluable population was defined as all participants who received at least one dose of study drug. For phase II, only one tumor type cohort was opened (LGG).
9999999, 0.0 to 9999999 = no participants experienced an event and DOR wasn't reached.

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

End point timeframe:

From first occurrence of objective response to disease progression or death due to any cause, whichever occurs first (up to 5 years, 2 months)

| **End point values** | Low Grade Glioma (Phase II) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (0.0 to 9999999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS) for Participants with Neuroblastoma (Phase I)

| End point title | Overall Survival (OS) for Participants with Neuroblastoma (Phase I) |
|---|---|

End point description:

OS was defined as the time from initiation of study drug to death from any cause. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.
0.0 to 9999999 = The 95% confidence interval could not be calculated from the data of one participant.

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

End point timeframe:

Baseline until death due to any cause (up to 5 years, 2 months)

| **End point values** | Neuroblastoma | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.6 (0.0 to 9999999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: OS for Participants with High-Grade Glioma (HGG) (Phase I) and Low-Grade Glioma (LGG) (Phase I and II)

| End point title | OS for Participants with High-Grade Glioma (HGG) (Phase I) and Low-Grade Glioma (LGG) (Phase I and II) |
|---|---|

End point description:

OS was defined as the time from initiation of study drug to death from any cause. While the data for LGG in the phase II cohort is presented separately in other parts of the record, it was also considered useful to combine the data for LGG from phase I and phase II, which was done here. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. For phase II, only one tumor type cohort was opened (LGG). As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.
9999999 = The upper limit cannot be calculated due to insufficient number of events. (HGG)
9999999, 0.0 to 9999999 = No participants experienced an event and DOR was not reached (LGG)

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

End point timeframe:

Baseline until death due to any cause (up to 5 years, 2 months)

| End point values | High Grade Glioma | Low Grade Glioma (Phase I and II) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 32 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 1.4 (0.6 to 9999999) | 9999999 (0.0 to 9999999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: OS for Participants with All Other Tumours (Phase I)

| End point title | OS for Participants with All Other Tumours (Phase I) |
|---|---|

End point description:

OS was defined as the time from initiation of study drug to death from any cause. The safety evaluable population was defined as all participants who received at least one dose of study drug. Participants enrolled into phase I (Dose-Escalation) cohorts independent of their tumor type. As the same criteria were not used to assess response in all tumor types, the efficacy analyses were broken down by tumor type.
9999999 = The median and 95% confidence interval could not be calculated from the data due to insufficient number of participants with events.

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

End point timeframe:

Baseline until death due to any cause (up to 5 years, 2 months)

| End point values | Dnet In Noonan's Syn Tumr (RAS/RAF/MEK /ERK Pathway Activation) | Malignant Peripheral Nerve Sheath Tumor | Metstic Mdstnl Ylksc Tumr (RAS/RAF/MEK /ERK Pathway Activation) | Non-Rhabdomyosarcoma Soft Tissue Sarcoma |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 2 | 1 | 1 |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (0.0 to 9999999) | 5.5 (0.8 to 9999999) | 1.1 (0.0 to 9999999) | 6.3 (0.0 to 9999999) |

| End point values | Plexiform Neurofibroma | Rhabdoid Tumor/ATRT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 1 | | |

| | | | | |
|---|---|---|---|---|
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (0.0 to 9999999) | 5.1 (0.0 to 9999999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Plasma Concentration Observed (Cmax) of Cobimetinib

| End point title | Maximum Plasma Concentration Observed (Cmax) of Cobimetinib |
|---|---|

End point description:

Plasma samples for determination of Cobimetinib concentration were collected prior to dosing and at 2, 4, 6 and 24 hours after dosing on Days 1 and 21 of Cycle 1. The sampling will allow determination of Cmax.

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

End point timeframe:

Pre-dose, 2, 4, 6, and 24 hours post-dose on Cycle 1 Days 1 and 21 (predose=within 4 hours prior to dose; cycle length=28 days)

| **End point values** | Phase I (Tablet) Cobimetinib (0.6 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (0.6 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 6 | 6 | 6 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Day 1 (n= 6,5,6,6,7,8,4,9) | 62.0 (± 82.3) | 88.3 (± 102) | 144 (± 58.6) | 51.5 (± 73.4) |
| Cycle 1 Day 21 (n= 5,5,6,6,7,8,4,9) | 51.1 (± 74.0) | 181 (± 134) | 193 (± 35.0) | 105 (± 84.5) |

| **End point values** | Phase I (Suspension) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1.33 mg/kg) (PK Population) | Phase II (Suspension) Cobimetinib (1 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 5 | 12 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Day 1 (n= 6,5,6,6,7,8,4,9) | 67.4 (± 165) | 136 (± 80.3) | 111 (± 37.0) | 44.0 (± 69.8) |
| Cycle 1 Day 21 (n= 5,5,6,6,7,8,4,9) | 156 (± 91.2) | 179 (± 113) | 172 (± 60.3) | 116 (± 42) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Cmax (Tmax) of Cobimetinib

| End point title | Time to Cmax (Tmax) of Cobimetinib |
|---|---|

End point description:

Plasma samples for determination of Cobimetinib concentration will be collected prior to dosing and at 2, 4, 6 and 24 hours after dosing on Days 1 and 21 of Cycle 1. The sampling will allow determination of Tmax.

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

End point timeframe:

Pre-dose, 2, 4, 6, and 24 hours post-dose on Cycle 1 Days 1 and 21 (pre-dose=within 4 hours prior to dose; cycle length=28 days)

| **End point values** | Phase I (Tablet) Cobimetinib (0.6 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (0.6 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 6 | 6 | 6 |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 6,5,6,6,7,8,4,9) | 4 (2 to 6) | 2 (2 to 6) | 3 (2 to 4) | 4 (2 to 6) |
| Cycle 1 Day 21 (n= 5,5,5,6,6,8,2,9) | 4 (2 to 6) | 4 (2 to 6) | 2 (2 to 4) | 4 (2 to 6) |

| **End point values** | Phase I (Suspension) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1.33 mg/kg) (PK Population) | Phase II (Suspension) Cobimetinib (1 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 5 | 12 |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n= 6,5,6,6,7,8,4,9) | 4 (2 to 6) | 2 (2 to 4) | 5 (2 to 6) | 4 (2 to 6) |
| Cycle 1 Day 21 (n= 5,5,5,6,6,8,2,9) | 2 (2 to 4) | 3 (2 to 6) | 4 (4 to 4) | 2 (2 to 6) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration-Time Curve From 0 to 24 Hours (AUC0-24) of Cobimetinib

| End point title | Area Under the Concentration-Time Curve From 0 to 24 Hours (AUC0-24) of Cobimetinib |
|---|---|

End point description:

Plasma samples for determination of Cobimetinib concentration were collected prior to dosing and at 2, 4, 6 and 24 hours after dosing on Days 1 and 21 of Cycle 1. The sampling will allow determination of AUC0-24.

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

End point timeframe:

Pre-dose, 2, 4, 6, and 24 hours post-dose on Cycle 1 Days 1 and 21 (pre-dose=within 4 hours prior to dose; cycle length=28 days)

| End point values | Phase I (Tablet) Cobimetinib (0.6 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (0.6 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 6 | 6 | 6 |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Day 1 (n= 6,5,6,6,6,8,3,9) | 865 (± 83.0) | 1006 (± 100) | 1432 (± 50.0) | 743 (± 67.4) |
| Cycle 1 Day 21 (n= 5,5,5,6,6,8,2,9) | 836 (± 83.5) | 2802 (± 111) | 2382 (± 38.4) | 1624 (± 80.4) |

| End point values | Phase I (Suspension) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1.33 mg/kg) (PK Population) | Phase II (Suspension) Cobimetinib (1 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 5 | 12 |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Day 1 (n= 6,5,6,6,6,8,3,9) | 1111 (± 144) | 1627 (± 74.0) | 1567 (± 33.1) | 589 (± 79.5) |
| Cycle 1 Day 21 (n= 5,5,5,6,6,8,2,9) | 1805 (± 109) | 2562 (± 104) | 2511 (± 104) | 1402 (± 59) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent Clearance (CL/F) of Cobimetinib

| End point title | Apparent Clearance (CL/F) of Cobimetinib |
|---|---|

End point description:

Plasma samples for determination of Cobimetinib concentration were collected prior to dosing and at 2, 4, 6 and 24 hours after dosing on Days 1 and 21 of Cycle 1, and within 4 hours prior to dosing on Day 1 of Cycle 2. Please note that for this Outcome Measure, the Apparent Clearance of Cobimetinib could not be calculated/estimated as PK samples were collected only up to 24hr post dosing.
9999999 = The Apparent Clearance of Cobimetinib could not be calculated/estimated as PK samples were collected only up to 24hr post dosing which resulted in insufficient data to calculate CL/F.

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

End point timeframe:

Pre-dose, 2, 4, 6, and 24 hours post-dose on Cycle 1 Days 1 and 21; pre-dose on Cycle 2 Day 1 (pre-dose=within 4 hours prior to dose; cycle length=28 days)

| **End point values** | Phase I (Tablet) Cobimetinib (0.6 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Tablet) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (0.6 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 6 | 6 | 6 |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 9999999 (± 9999999) | 9999999 (± 9999999) | 9999999 (± 9999999) | 9999999 (± 9999999) |

| **End point values** | Phase I (Suspension) Cobimetinib (0.8 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1 mg/kg) (PK Population) | Phase I (Suspension) Cobimetinib (1.33 mg/kg) (PK Population) | Phase II (Suspension) Cobimetinib (1 mg/kg) (PK Population) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 5 | 12 |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 9999999 (± 9999999) | 9999999 (± 9999999) | 9999999 (± 9999999) | 9999999 (± 9999999) |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Baseline up until 30 days after the last dose of study drug (up to 5 years, 2 months) | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Phase I (Tablet) Cobimetinib (0.6 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Tablet) Cobimetinib (0.8 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Tablet) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (0.6 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.6 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (0.8 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 0.8 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase I (Suspension) Cobimetinib (1.33 mg/kg) |
| Reporting group description: | |
| Dose-Escalation: Participants received 1.33 milligrams per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |
| Reporting group title | Phase II (Suspension) Cobimetinib (1 mg/kg) |
| Reporting group description: | |
| Dose-Expansion: Participants received 1 milligram per kilogram (mg/kg) cobimetinib orally once daily on Days 1 to 21 of each 28-day treatment cycle. | |

| Serious adverse events | Phase I (Tablet) Cobimetinib (0.6 mg/kg) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) | Phase I (Tablet) Cobimetinib (1 mg/kg) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 2 / 6 (33.33%) |
| number of deaths (all causes) | 2 | 2 | 1 |
| number of deaths resulting from | 0 | 0 | 0 |

| adverse events | | | |
|---|---|---|---|
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (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 |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (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 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (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 | | | |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (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 |

| | | | |
|---|---|---|---|
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Phase I (Suspension) Cobimetinib (0.6 mg/kg) | Phase I (Suspension) Cobimetinib (1 mg/kg) | Phase I (Suspension) Cobimetinib (0.8 mg/kg) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 8 (25.00%) | 1 / 7 (14.29%) |
| number of deaths (all causes) | 2 | 2 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (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 | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (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 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Phase I (Suspension) Cobimetinib (1.33 mg/kg) | Phase II (Suspension) Cobimetinib (1 mg/kg) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 5 / 12 (41.67%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| 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 | | | |
| Femoral neck fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Phase I (Tablet) Cobimetinib (0.6 mg/kg) | Phase I (Tablet) Cobimetinib (0.8 mg/kg) | Phase I (Tablet) Cobimetinib (1 mg/kg) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 6 / 6 (100.00%) | 6 / 6 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hair follicle tumour benign | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 3 / 6 (50.00%) |
| occurrences (all) | 2 | 2 | 5 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Xerosis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nodule | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Extravasation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 2 | 3 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scrotal ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Epistaxis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 3 | 1 | 2 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 1 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 6 (33.33%) | 1 / 6 (16.67%) |
| occurrences (all) | 3 | 4 | 1 |
| Sputum decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Behaviour disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anxiety | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Inappropriate affect | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bradyphrenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Blood bicarbonate decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood chloride increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 9 | 0 |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anion gap increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cortisol decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Mean cell volume increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 3 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 2 |
| Face injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Foreign body in ear | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Head injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 5 |

| | | | |
|---|---|---|---|
| Skin laceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Fall | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 4 |
| Abdominal injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin wound | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Iris hamartoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 6 (50.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 5 | 4 | 2 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 4 |
| Tremor | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Lethargy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ocular hyperaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Punctate keratitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ocular hypertension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Miosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Detachment of retinal pigment epithelium | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Optic disc disorder | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Visual acuity reduced transiently | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Serous retinal detachment | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Retinal disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Corneal neovascularisation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Optic atrophy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Visual impairment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual field defect | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelid skin dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Eyelid ptosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chorioretinopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Lip haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 6 (33.33%) | 4 / 6 (66.67%) |
| occurrences (all) | 1 | 4 | 9 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 6 (33.33%) | 3 / 6 (50.00%) |
| occurrences (all) | 3 | 3 | 5 |
| Lip ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 3 / 6 (50.00%) |
| occurrences (all) | 2 | 1 | 3 |
| Gastrooesophageal reflux disease | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Faeces hard | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth impacted | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 6 (50.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 3 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 4 / 6 (66.67%) | 5 / 6 (83.33%) |
| occurrences (all) | 5 | 17 | 8 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anorectal discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Papule | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 6 (33.33%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 5 | 2 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Telangiectasia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Eczema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acne | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eczema asteatotic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hirsutism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Xeroderma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hand dermatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Miliaria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Dandruff | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seborrhoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 6 (16.67%) | 2 / 6 (33.33%) |
| occurrences (all) | 6 | 2 | 2 |
| Erythema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Pityriasis alba | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Urinary hesitation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Polyuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Endocrine disorders | | | |
| Precocious puberty | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 1 | 6 |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 6 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 4 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Spinal deformity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Scarlet fever | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral tonsillitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Fungal skin infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 5 |

| | | | |
|---|---|---|---|
| Varicella | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Impetigo | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 6 (16.67%) | 2 / 6 (33.33%) |
| occurrences (all) | 1 | 1 | 2 |

| **Non-serious adverse events** | Phase I (Suspension) Cobimetinib (0.6 mg/kg) | Phase I (Suspension) Cobimetinib (1 mg/kg) | Phase I (Suspension) Cobimetinib (0.8 mg/kg) |
|---|---|---|---|
| Total subjects affected by non-serious | | | |

| adverse events | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 6 (100.00%) | 8 / 8 (100.00%) | 7 / 7 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hair follicle tumour benign | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 8 (37.50%) | 2 / 7 (28.57%) |
| occurrences (all) | 2 | 3 | 3 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Xerosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nodule | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Extravasation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 8 (25.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 2 | 1 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Scrotal ulcer | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vulvovaginal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 8 (25.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 1 | 1 |
| Sputum decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Behaviour disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Inappropriate affect | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Bradyphrenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Blood bicarbonate decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 3 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood chloride increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 0 | 3 |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anion gap increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 4 | 1 | 1 |
| Weight decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Body temperature decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cortisol decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 0 | 3 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 | 1 |
| Mean cell volume increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 2 / 7 (28.57%) |
| occurrences (all) | 1 | 1 | 3 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 | 1 |
| Face injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thermal burn | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Foreign body in ear | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin wound | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Iris hamartoma | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 4 / 8 (50.00%) | 3 / 7 (42.86%) |
| occurrences (all) | 4 | 4 | 8 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 8 (25.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 8 (25.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Punctate keratitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ocular hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Miosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Detachment of retinal pigment epithelium | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Optic disc disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual acuity reduced transiently | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Serous retinal detachment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Retinal disorder | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Corneal neovascularisation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Optic atrophy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Eye disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Visual field defect | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid skin dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid ptosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chorioretinopathy | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Lip haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 4 / 8 (50.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 2 | 7 | 9 |
| Anal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 8 (25.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Lip ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 8 (37.50%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 5 | 7 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dental caries | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Faeces hard | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth impacted | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 2 / 7 (28.57%) |
| occurrences (all) | 1 | 1 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 8 (50.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 6 | 6 | 3 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Anorectal discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Papule | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 2 / 7 (28.57%) |
| occurrences (all) | 1 | 1 | 2 |

| | | | |
|---|---|---|---|
| Skin fissures | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Telangiectasia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 1 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acne | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Eczema asteatotic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hirsutism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Xeroderma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Onychomadesis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hand dermatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Miliaria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dandruff | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Alopecia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seborrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 1 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 8 (25.00%) | 3 / 7 (42.86%) |
| occurrences (all) | 0 | 2 | 3 |
| Erythema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Pityriasis alba | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary hesitation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Polyuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Precocious puberty | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 1 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 0 | 3 |
| Back pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 8 (25.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 2 | 1 |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 8 (25.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Groin pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Spinal deformity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Scarlet fever | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral tonsillitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 1 | 1 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Varicella | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 | 1 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 | 1 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Hordeolum | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Impetigo | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nail infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 8 (12.50%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 5 | 0 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 8 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 8 (25.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 2 | 2 |

| **Non-serious adverse events** | Phase I (Suspension) Cobimetinib (1.33 mg/kg) | Phase II (Suspension) Cobimetinib (1 mg/kg) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 5 (100.00%) | 12 / 12 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Hair follicle tumour benign | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Xerosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nodule | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Mucosal inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Extravasation | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 3 / 12 (25.00%) | |
| occurrences (all) | 3 | 5 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Scrotal ulcer | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vulvovaginal pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 4 / 12 (33.33%) | |
| occurrences (all) | 1 | 5 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 3 / 12 (25.00%) | |
| occurrences (all) | 0 | 5 | |
| Sputum decreased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Behaviour disorder | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Inappropriate affect | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Bradyphrenia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Blood bicarbonate decreased | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 2 | | |
| Ejection fraction decreased | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Blood alkaline phosphatase increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 2 | | |
| Blood chloride increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 3 | | |
| Aspartate aminotransferase increased | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 2 | 1 | | |
| White blood cell count decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | | |
| occurrences (all) | 0 | 8 | | |
| Blood creatinine decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 1 | | |
| Electrocardiogram QT prolonged | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Anion gap increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 3 | | |
| Lymphocyte count decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | | |
| occurrences (all) | 0 | 4 | | |
| Weight decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Body temperature decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |

| | | | | |
|---|---|---|---|---|
| Platelet count increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 2 | | |
| Cortisol decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Intraocular pressure increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Neutrophil count decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 5 | | |
| Transaminases increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Gamma-glutamyltransferase increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Protein total decreased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 3 | | |
| Blood creatinine increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Mean cell volume increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 1 | | |
| Lymphocyte count increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Blood creatine phosphokinase increased | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 4 / 12 (33.33%) | | |
| occurrences (all) | 0 | 8 | | |
| White blood cell count increased | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Face injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Wrist fracture | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | 1 | | |
| Foreign body in ear | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Hand fracture | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Contusion | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Limb injury | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Arthropod bite | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Ligament sprain | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Foot fracture | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Head injury | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Skin laceration | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Tooth fracture | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Fall | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | 1 | | |
| Abdominal injury | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin wound | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Congenital, familial and genetic disorders | | | |
| Iris hamartoma | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 7 / 12 (58.33%) | |
| occurrences (all) | 5 | 11 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 3 / 12 (25.00%) | |
| occurrences (all) | 0 | 6 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Punctate keratitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Ocular hypertension | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Miosis | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Detachment of retinal pigment epithelium | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Optic disc disorder | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Visual acuity reduced transiently | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Serous retinal detachment | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Retinal disorder | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Corneal neovascularisation | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 1 | | |
| Optic atrophy | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 1 | | |
| Dry eye | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Visual impairment | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Eye pain | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Eye disorder | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |

| | | | |
|---|---|---|---|
| Visual field defect | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eyelid skin dryness | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eyelid ptosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 4 | 2 | |
| Lip haemorrhage | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 7 / 12 (58.33%) | |
| occurrences (all) | 2 | 14 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 5 (20.00%) | 3 / 12 (25.00%) | |
| occurrences (all) | 1 | 3 | |
| Lip ulceration | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal distension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Faeces hard | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Tooth impacted | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 3 / 12 (25.00%) | |
| occurrences (all) | 2 | 7 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | 4 / 12 (33.33%) | |
| occurrences (all) | 10 | 11 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Anorectal discomfort | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Papule | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash papular | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Telangiectasia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eczema | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Acne | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eczema asteatotic | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hirsutism | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Xeroderma | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hand dermatitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash macular | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Miliaria | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Dandruff | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Skin mass | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Seborrhoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Purpura | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 3 | 1 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 2 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pityriasis alba | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary hesitation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Urinary tract pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Micturition urgency | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Polyuria | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Precocious puberty | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Muscle spasms | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Spinal deformity | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Scarlet fever | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral tonsillitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Varicella | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |

| | | | | |
|---|---|---|---|---|
| Localised infection | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Rhinovirus infection | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Skin infection | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Ear infection | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Viral upper respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Oral herpes | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| H1N1 influenza | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 1 | | |
| Folliculitis | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Oral candidiasis | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |
| Nasopharyngitis | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 12 (16.67%) | | |
| occurrences (all) | 0 | 2 | | |
| Suspected COVID-19 | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | | |
| occurrences (all) | 0 | 1 | | |
| Hordeolum | | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | 0 | | |

| | | | |
|---|---|---|---|
| Influenza | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Impetigo | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nail infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Otitis media | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypophosphataemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 18 May 2015 | Following updates were made: [1] Addition of complete rationale for using both tablet and liquid formulations; [2] Modification of guidance regarding frequency and nature of ophthalmology examinations; [3] Clarification of PK Outcome Measure; [4] Updates to Inclusion/Exclusion Criteria and [5] Addition of Safety Analysis. |
| 05 August 2015 | Following updates were made: [1] Removal of Liquid Formulation from study, so only Tablet Formulation to be kept; [2] Addition of Enrolment restrictions; [3] Modification of Dose Escalation rules; [4] Change in Starting Dose of Dose Escalation from 0.8 mg/kg/day to 0.6 mg/kg/day and [5] Dose-Limiting Toxicity (DLT) updates. |
| 02 February 2016 | Following updates were made: [1] Removal of references to perception of clinical benefit; [2] Updating of cardiac function DLT rules; [3] Updating of Intrapatient dose escalation guidance and [4] Clarification of Dose reduction guidance. |
| 15 June 2016 | Following updates were made: [1] Addition of new Suspension Formulation; [2] Updates to Safety Information regarding Cobimetinib and [3] Additional Study Changes. |
| 03 November 2016 | Following updates were made: [1] Updated to align with most current available data with regards to the risks associated to Cobimetinib; [2] Updates to list of defined DLTs during the Dose Escalation phase; [3] Addition of new Eligibility Criteria; [4] Modification to International Neuroblastoma Response Criteria (INRC) used in this study; [5] Clarification of de-escalation rules and [6] Clarifications to Appendix 1. |
| 07 February 2017 | Following updates were made: [1] Restoration of dose modification guidance; [2] Clarification to Inclusion criteria and [3] Additional information relating to intracerebral hemorrhage. |
| 10 May 2017 | Following updates were made: [1] Revisions made to determination of the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) of each Cobimetinib formulation (tablet and suspension); [2] Clarification that enrolment of expansion cohorts may begin only after the IMC has reviewed pharmacokinetic (PK) and safety data and [3] Updates to include rationale for requiring a separate suspension dose escalation beginning at one level below that of the tablet MTD/MAD. |
| 09 May 2018 | Following updates were made: [1] Incorporation of Response Assessment in Neuro-Oncology (RANO) criteria for LGG; [2] Update to Inclusion Criteria; [3] Number of Study Subjects increased to approximately 70; [4] Updates to the interim efficacy analyses; [5] Updates to study stopping rules; [6] Clarification to Exclusion Criteria and [7] Updates to Appendix 5 and 10. |
| 06 July 2018 | Following update was made: [1] The objective response rate (ORR) for low-grade glioma (LGG) incorporating minor response, has been made an exploratory endpoint. |
| 11 April 2019 | Following updates were made: [1] Reduction in the frequency of tumor assessments for subjects who have completed at least 12 cycles of Cobimetinib therapy; [2] Plasma samples collection updated to align with the new tumor assessments schedule; [3] Reduction in the frequency of ophthalmologic examinations for subjects who have completed 6 cycles of Cobimetinib therapy and [4] Updates to Appendix 1 and 10. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported