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 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 Units: Years			
arithmetic mean	11.8	9.5	9.5
standard deviation	± 3.5	± 3.3	± 3.4
Sex: Female, Male Units:			
Female	1	2	4
Male	5	4	2
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	5	3	4
Not Stated	0	2	2
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	0
Black or African American	0	1	1
Unknown	1	1	2
White	5	4	3
Tumor Type 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 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 Units: Years			
arithmetic mean	8.5	9.7	8.9
standard deviation	± 1.4	± 5.3	± 3.1
Sex: Female, Male Units:			
Female	2	0	2
Male	4	7	6
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	2	1
Not Hispanic or Latino	1	2	4
Not Stated	4	3	3
Race/Ethnicity, Customized Units: Subjects			
Asian	0	1	0
Black or African American	1	0	0
Unknown	5	4	3
White	0	2	5
Tumor Type 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 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 Units: Years			
arithmetic mean	10.2	8.7	
standard deviation	± 3.3	± 7.5	-
Sex: Female, Male Units:			
Female	5	7	23
Male	0	5	33
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	4	11
Not Hispanic or Latino	3	7	29
Not Stated	1	1	16
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	1
Black or African American	0	0	3
Unknown	1	1	18
White	4	11	34
Tumor Type 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 (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)[4]

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:

[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	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 (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)[5]

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:

[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	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 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: 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: 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: 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			

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			

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