Clinical trial results:
Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects with Advanced BRAF V600-Mutation Positive Solid Tumors

Summary

EudraCT number	2012-001499-12
Trial protocol	GB Outside EU/EEA ES DE DK IT
Global end of trial date	04 December 2020

Results information

Result version number	v1
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	116013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01677741
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CDRB436A2102

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001147-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2020
Global end of trial reached?	Yes
Global end of trial date	04 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the safe and tolerable dabrafenib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures to the dabrafenib adult dose, in subjects with BRAF V600 mutation positive tumors

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	85
EEA total number of subjects	27

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)	3
Children (2-11 years)	47
Adolescents (12-17 years)	35
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 19 centers in eight participating countries: Australia (1), Canada (1), Denmark (1), Germany (1), France (4), Spain (1), United Kingdom (2), and United States (8).

Pre-assignment

Screening details:

Patients participated in only either Part 1 (Dose Escalation) or Part 2 (Tumor specific expansion) of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)

Arm description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Arm title	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)

Arm description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Arm title	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)

Arm description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Arm title	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)

Arm description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Arm title	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)

Arm description:

Subjects with low-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Arm type	Experimental

Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Arm title	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)

Arm description:

Subjects with high-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Arm title	Part 2 (Tumor specific expansion): Cohort 3 (LCH)

Arm description:

Subjects with Langerhans cell histiocytosis (LCH) with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Arm title	Part 2 (Tumor specific expansion): Cohort 4 (Other)

Arm description:

Subjects with other tumors with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice

daily till end of study.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436
Pharmaceutical forms	Dispersible tablet, Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study used both oral solid dose formulations as well as oral liquid dose formulations. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules, for children who were able to swallow capsules. Two lower strength capsules (10 mg and 25 mg) were also used initially but were discontinued during the course of the study. The total daily dose was not to exceed 300 mg (150 mg BID). The oral liquid formulation was initially a powder for oral suspension (stick pack) and was replaced by dispersible tablets for oral suspension during the course of the study. The oral liquid formulations were to be used by all subjects with difficulty swallowing solid dose forms or were at risk of choking.

Number of subjects in period 1	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
Started	3	10	8
DLT evaluable population	3	10	8
PK population	3	10	8
Completed	0	0	0
Not completed	3	10	8
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	2	7	5
Enrolled in a rollover study	-	3	2
Progressive disease	1	-	1

Number of subjects in period 1	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)
Started	6	17	28
DLT evaluable population	6	0	0
PK population	6	17	28
Completed	0	0	0
Not completed	6	17	28
Adverse event, serious fatal	1	-	1
Consent withdrawn by subject	4	11	20
Enrolled in a rollover study	1	6	6
Progressive disease	-	-	1

Number of subjects in period 1	Part 2 (Tumor specific expansion): Cohort 3 (LCH)	Part 2 (Tumor specific expansion): Cohort 4 (Other)

Started	11	2
DLT evaluable population	0	0
PK population	11	2
Completed	0	0
Not completed	11	2
Adverse event, serious fatal	-	-
Consent withdrawn by subject	4	2
Enrolled in a rollover study	7	-
Progressive disease	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)
Reporting group description:	
Subjects with low-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	
Reporting group title	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)
Reporting group description:	
Subjects with high-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	
Reporting group title	Part 2 (Tumor specific expansion): Cohort 3 (LCH)
Reporting group description:	
Subjects with Langerhans cell histiocytosis (LCH) with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	
Reporting group title	Part 2 (Tumor specific expansion): Cohort 4 (Other)
Reporting group description:	
Subjects with other tumors with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	

Reporting group values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)

Number of subjects	3	10	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	1
Children (2-11 years)	2	4	6
Adolescents (12-17 years)	1	6	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	9.33	11.30	6.58
standard deviation	± 5.132	± 5.355	± 5.445
Sex: Female, Male Units: Participants			
Female	1	5	3
Male	2	5	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	2	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	3	8	7
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)
Number of subjects	6	17	28
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	9	10
Adolescents (12-17 years)	0	8	18
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	7.17	9.65	12.32
standard deviation	± 3.189	± 5.195	± 3.692
Sex: Female, Male			
Units: Participants			
Female	3	8	11
Male	3	9	17
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	2	3
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	0	2	1
White	6	13	22
More than one race	0	0	1
Unknown or Not Reported	0	0	0

Reporting group values	Part 2 (Tumor specific expansion): Cohort 3 (LCH)	Part 2 (Tumor specific expansion): Cohort 4 (Other)	Total
Number of subjects	11	2	85
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)	2	0	3
Children (2-11 years)	9	1	47
Adolescents (12-17 years)	0	1	35
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	5.52	9.50	
standard deviation	± 3.390	± 10.607	-
Sex: Female, Male			
Units: Participants			
Female	4	0	35
Male	7	2	50
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	7
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	0	0	4
White	11	2	72
More than one race	0	0	1
Unknown or Not Reported	0	0	0

Subject analysis sets

Subject analysis set title	Part 1 (Dose Escalation): Dabrafenib treatment (All Patients)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients from all dose levels (3 mg/kg, 3.75 mg/kg, 4.5 mg/kg and 5.25 mg/kg) were pooled together

Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together and receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together and receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together

Subject analysis set title	All LGG subjects at Recommended Phase 2 dose (RP2D)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All LGG subjects who have been assigned to RP2D across Part 1 and Part 2

Subject analysis set title	All LGG subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All LGG subjects across Part 1 and Part 2

Subject analysis set title	All HGG subjects at Recommended Phase 2 dose (RP2D)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All HGG subjects who have been assigned to RP2D across Part 1 and Part 2

Subject analysis set title	All HGG subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All HGG subjects across Part 1 and Part 2

Subject analysis set title	All enrolled participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects who received at least one dose of study treatment across Part 1 and Part 2 were pooled together

Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients from in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together and receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Reporting group values	Part 1 (Dose Escalation): Dabrafenib treatment (All Patients)	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)
Number of subjects	27	27	31
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	±	±	±
Sex: Female, Male Units: Participants			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	Part 2 (Tumor Specific Expansion): All patients	All LGG subjects at Recommended Phase 2 dose (RP2D)	All LGG subjects
Number of subjects	58	24	33
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	 ±	 17 ±	 24 ±
Sex: Female, Male Units: Participants			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	All HGG subjects at Recommended Phase 2 dose (RP2D)	All HGG subjects	All enrolled participants
Number of subjects	28	35	85
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	 7 ±	 10 ±	 0.223 ±
Sex: Female, Male Units: Participants			
Female Male			

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)		
Number of subjects	31		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	 ±		
Sex: Female, Male Units: Participants			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Reporting group description:	
Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.	
Reporting group title	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)
Reporting group description:	
Subjects with low-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	
Reporting group title	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)
Reporting group description:	
Subjects with high-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	
Reporting group title	Part 2 (Tumor specific expansion): Cohort 3 (LCH)
Reporting group description:	
Subjects with Langerhans cell histiocytosis (LCH) with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	
Reporting group title	Part 2 (Tumor specific expansion): Cohort 4 (Other)
Reporting group description:	
Subjects with other tumors with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	
Subject analysis set title	Part 1 (Dose Escalation): Dabrafenib treatment (All Patients)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from all dose levels (3 mg/kg, 3.75 mg/kg, 4.5 mg/kg and 5.25 mg/kg) were pooled together	
Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together and receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together and receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together

Subject analysis set title	All LGG subjects at Recommended Phase 2 dose (RP2D)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All LGG subjects who have been assigned to RP2D across Part 1 and Part 2

Subject analysis set title	All LGG subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All LGG subjects across Part 1 and Part 2

Subject analysis set title	All HGG subjects at Recommended Phase 2 dose (RP2D)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All HGG subjects who have been assigned to RP2D across Part 1 and Part 2

Subject analysis set title	All HGG subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All HGG subjects across Part 1 and Part 2

Subject analysis set title	All enrolled participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects who received at least one dose of study treatment across Part 1 and Part 2 were pooled together

Subject analysis set title	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients from in all 4 tumor-specific pediatric populations (Cohort 1 Low-Grade Gliomas (LGG), Cohort 2 High-Grade Gliomas (HGG), Cohort 3 Langerhans cell histiocytosis (LCH) and Cohort 4 Miscellaneous tumors including melanoma and papillary thyroid carcinoma (Other)) were pooled together and receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Primary: Incidence of treatment emergent Adverse Events (AEs) in Part 1 (Dose Escalation)

End point title	Incidence of treatment emergent Adverse Events (AEs) in Part 1 (Dose Escalation)[1][2]

End point description:

The distribution of adverse events will be done via the analysis of frequencies for treatment emergent Adverse Events, Serious Adverse Events and Deaths due to AEs, through the monitoring of relevant

clinical and laboratory safety parameters. Only descriptive analysis performed.

End point type	Primary

End point timeframe:

From study treatment start date till 30 days safety follow-up, assessed up to approximately 90 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: Only descriptive analysis performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	10	8	6
Units: Participants				
All deaths (All grades)	0	0	0	1
All deaths (Grades 3/4/5)	0	0	0	1
On-treatment deaths (All grades)	0	0	0	1
On-treatment deaths (Grades 3/4/5)	0	0	0	1
Adverse Events (AEs) (All grades)	3	10	8	6
Adverse Events (AEs) (Grades 3/4/5)	1	6	5	5
AEs suspected to be drug related (All grades)	3	10	8	5
AEs suspected to be drug related (Grades 3/4/5)	0	3	2	3
Serious Adverse Events (SAEs) (All grades)	0	5	5	3
Serious Adverse Events (SAEs) (Grades 3/4/5)	0	4	4	3
SAEs suspected to be drug related (All grades)	0	2	2	1
SAEs suspected to be drug related (Grades 3/4/5)	0	2	1	1
Fatal SAEs (All grades)	0	0	0	1
Fatal SAEs (Grades 3/4/5)	0	0	0	1
AEs leading to discontinuation (All grades)	0	0	1	0
AEs leading to discontinuation (Grades 3/4/5)	0	0	1	0
AEs requiring dose interruptions (All grades)	1	5	6	5
AEs requiring dose interruptions (Grades 3/4/5)	1	4	3	4
AEs requiring dose reductions (All grades)	0	2	3	1
AEs requiring dose reductions (Grades 3/4/5)	0	2	2	1

End point values	Part 1 (Dose Escalation): Dabrafenib			

	treatment (All Patients)			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: Participants				
All deaths (All grades)	1			
All deaths (Grades 3/4/5)	1			
On-treatment deaths (All grades)	1			
On-treatment deaths (Grades 3/4/5)	1			
Adverse Events (AEs) (All grades)	27			
Adverse Events (AEs) (Grades 3/4/5)	17			
AEs suspected to be drug related (All grades)	26			
AEs suspected to be drug related (Grades 3/4/5)	8			
Serious Adverse Events (SAEs) (All grades)	13			
Serious Adverse Events (SAEs) (Grades 3/4/5)	11			
SAEs suspected to be drug related (All grades)	5			
SAEs suspected to be drug related (Grades 3/4/5)	4			
Fatal SAEs (All grades)	1			
Fatal SAEs (Grades 3/4/5)	1			
AEs leading to discontinuation (All grades)	1			
AEs leading to discontinuation (Grades 3/4/5)	1			
AEs requiring dose interruptions (All grades)	17			
AEs requiring dose interruptions (Grades 3/4/5)	12			
AEs requiring dose reductions (All grades)	6			
AEs requiring dose reductions (Grades 3/4/5)	5			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum concentration (Cmax) of dabrafenib

End point title	Maximum concentration (Cmax) of dabrafenib[3][4]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. Cmax of dabrafenib was listed and summarized using descriptive statistics.

End point type	Primary

End point timeframe:

Week 1 Day 1, Week 3 Day 15

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: Only descriptive analysis performed.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	10	8	6
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 (n=2,10,8,6,27,31)	1890 (± 678)	1440 (± 787)	2200 (± 1210)	2070 (± 1120)
Week 3 Day 15 (n=3,10,8,6,26,29)	1530 (± 526)	1390 (± 721)	1760 (± 1010)	1920 (± 1030)

End point values	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	31		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1 (n=2,10,8,6,27,31)	1640 (± 922)	1740 (± 806)		
Week 3 Day 15 (n=3,10,8,6,26,29)	1640 (± 763)	1440 (± 580)		

Statistical analyses

No statistical analyses for this end point

Primary: Area under the concentration-time curve over the dosing interval (AUC(0-τ)) and AUC from zero to infinity (AUC(0-inf)) of dabrafenib

End point title	Area under the concentration-time curve over the dosing interval (AUC(0-τ)) and AUC from zero to infinity (AUC(0-inf)) of dabrafenib[5][6]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. AUC(0-τ) and AUC(0-inf) of dabrafenib were to be listed and summarized using descriptive statistics. Due to limited dabrafenib PK data collected for Day 1 (up to 4 hours post-dose PK data only), no reliable AUC(0-t) and AUC (0-inf) PK parameters were collected/calculated.

End point type	Primary

End point timeframe:

Week 1 Day 1

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 reliable AUC(0-t) and AUC (0-inf) PK parameters were collected/calculated.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the

baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[7]	0[8]	0[9]	0[10]
Units: hr*ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[7] - No reliable AUC(0-t) and AUC (0-inf) PK parameters were collected/calculated.

[8] - No reliable AUC(0-t) and AUC (0-inf) PK parameters were collected/calculated.

[9] - No reliable AUC(0-t) and AUC (0-inf) PK parameters were collected/calculated.

[10] - No reliable AUC(0-t) and AUC (0-inf) PK parameters were collected/calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose (trough) concentration (C tau) of dabrafenib and its metabolites

End point title	Pre-dose (trough) concentration (C tau) of dabrafenib and its metabolites[11]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. Pre-dose (trough) concentration (C tau) was to be listed and summarized using descriptive statistics for dabrafenib and its metabolites (hydroxy-dabrafenib [GSK2285403], carboxy-dabrafenib [GSK2298683], and desmethyl-dabrafenib [GSK2167542]).

End point type	Secondary

End point timeframe:

Week 3 Day 15

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	10	8	6
Units: ng/mL				
arithmetic mean (standard deviation)				
dabrafenib (n=3,10,8,6,26,29)	22.1 (± 26.0)	82.1 (± 115.0)	76.6 (± 86.0)	12.6 (± 6.48)
hydroxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
carboxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
desmethyl-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

End point values	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	31		
Units: ng/mL				
arithmetic mean (standard deviation)				
dabrafenib (n=3,10,8,6,26,29)	71.4 (± 83.2)	54.7 (± 97.4)		
hydroxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)		
carboxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)		
desmethyl-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: The AUC(0-t) of dabrafenib metabolites

End point title	The AUC(0-t) of dabrafenib metabolites[12]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. Area under the time-concentration curve from time zero (pre-dose) to last time of quantifiable concentration (AUC[0-t]) dabrafenib metabolites (hydroxy-dabrafenib [GSK2285403], carboxy-dabrafenib [GSK2298683], and desmethyl-dabrafenib [GSK2167542]) were to be listed and summarized using descriptive statistics. Due to limited dabrafenib PK data collected for Day 1 (up to 4 hours post-dose PK data only), no reliable AUC(0-t) PK parameters were collected/calculated.

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 3 Day 15

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[13]	0[14]	0[15]	0[16]
Units: hr*ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[13] - No reliable AUC(0-t) PK parameters were collected/calculated.

[14] - No reliable AUC(0-t) PK parameters were collected/calculated.

[15] - No reliable AUC(0-t) PK parameters were collected/calculated.

[16] - No reliable AUC(0-t) PK parameters were collected/calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: The AUC(0-tau) of dabrafenib and its metabolites

End point title	The AUC(0-tau) of dabrafenib and its metabolites[17]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. Area under the time-concentration curve from time zero (pre-dose) to last time of quantifiable concentration (AUC(0-tau) of dabrafenib and its metabolites (hydroxy-dabrafenib [GSK2285403], carboxy-dabrafenib [GSK2298683], and desmethyl-dabrafenib [GSK2167542]) were to be listed and summarized using descriptive statistics. Due to limited dabrafenib PK data collected for Day 1 (up to 4 hours post-dose PK data only), no reliable AUC(0-t) PK parameters were collected/calculated.

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 3 Day 15

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[18]	0[19]	0[20]	0[21]
Units: hr*ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[18] - No reliable AUC(0-t) PK parameters were collected/calculated.

[19] - No reliable AUC(0-t) PK parameters were collected/calculated.

[20] - No reliable AUC(0-t) PK parameters were collected/calculated.

[21] - No reliable AUC(0-t) PK parameters were collected/calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent total clearance of the drug from plasma after oral administration (CL/F) of dabrafenib

End point title	Apparent total clearance of the drug from plasma after oral administration (CL/F) of dabrafenib[22]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. CL/F of dabrafenib was to be listed and summarized using descriptive statistics. Due to limited dabrafenib PK data collected for Day 1 (up to 4 hours post-dose PK data only), no reliable CL/F PK parameters were collected/calculated.

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 3 Day 15

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[23]	0[24]	0[25]	0[26]
Units: mL/hr				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[23] - No reliable CL/F PK parameters were collected/calculated.

[24] - No reliable CL/F PK parameters were collected/calculated.

[25] - No reliable CL/F PK parameters were collected/calculated.

[26] - No reliable CL/F PK parameters were collected/calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration (Cmax) of dabrafenib metabolites

End point title	Maximum concentration (Cmax) of dabrafenib metabolites[27]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. Cmax of dabrafenib metabolites (hydroxy-dabrafenib [GSK2285403], carboxy-dabrafenib [GSK2298683], and desmethyl-dabrafenib [GSK2167542]) were listed and summarized using descriptive statistics.

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 3 Day 15

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	10	8	6
Units: ng/mL				
arithmetic mean (standard deviation)				
hydroxy-dabrafenib @ Wk1D1 (n=2,10,8,6,26,31)	823 (± 199)	765 (± 398)	1060 (± 670)	1470 (± 597)
hydroxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	743 (± 362)	764 (± 225)	787 (± 263)	1120 (± 565)

carboxy-dabrafenib @ Wk1D1 (n=3,10,8,6,27,31)	1980 (± 1400)	1440 (± 637)	1550 (± 1370)	5040 (± 3630)
carboxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	5120 (± 2700)	6630 (± 1800)	10200 (± 3990)	11600 (± 3070)
desmethyl-dabrafenib @ Wk1D1 (n=3,10,8,6,21,27)	13.3 (± 3.53)	8.06 (± 5.11)	20.2 (± 14.6)	26.0 (± 11.3)
desmethyl-dabrafenib @ Wk3D15 (n=3,10,8,6,24,29)	356 (± 455)	399 (± 370)	730 (± 841)	256 (± 98.0)

End point values	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	31		
Units: ng/mL				
arithmetic mean (standard deviation)				
hydroxy-dabrafenib @ Wk1D1 (n=2,10,8,6,26,31)	828 (± 422)	1010 (± 475)		
hydroxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	851 (± 356)	767 (± 278)		
carboxy-dabrafenib @ Wk1D1 (n=3,10,8,6,27,31)	2520 (± 1960)	2980 (± 1760)		
carboxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	9070 (± 3990)	8320 (± 2570)		
desmethyl-dabrafenib @ Wk1D1 (n=3,10,8,6,21,27)	28.9 (± 77.0)	13.5 (± 11.3)		
desmethyl-dabrafenib @ Wk3D15 (n=3,10,8,6,24,29)	350 (± 125)	333 (± 207)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum (peak) plasma concentration following drug administration (Tmax) of dabrafenib and its metabolites

End point title	Time to reach maximum (peak) plasma concentration following drug administration (Tmax) of dabrafenib and its metabolites[28]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. Tmax was listed and summarized using descriptive statistics for dabrafenib and its metabolites (hydroxy-dabrafenib [GSK2285403], carboxy-dabrafenib [GSK2298683], and desmethyl-dabrafenib [GSK2167542]).

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 3 Day 15

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	10	8	6
Units: Hour (hr)				
median (full range (min-max))				
dabrafenib @ Wk1D1 (n=2,10,8,6,27,31)	2.00 (2.00 to 2.00)	2.00 (2.00 to 4.00)	2.00 (0.50 to 4.00)	2.00 (2.00 to 4.00)
dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	1.00 (1.00 to 2.00)	2.00 (0.50 to 4.00)	2.00 (1.00 to 3.00)	2.00 (1.00 to 3.00)
hydroxy-dabrafenib @ Wk1D1 (n=2,10,8,6,26,31)	4.00 (4.00 to 4.00)	4.00 (2.00 to 4.00)	3.00 (0.50 to 4.00)	3.00 (2.00 to 4.00)
hydroxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	2.00 (1.00 to 3.00)	2.50 (1.00 to 4.00)	2.00 (1.00 to 4.00)	2.00 (1.00 to 3.00)
carboxy-dabrafenib @ Wk1D1 (n=2,10,7,6,27,31)	4.00 (4.00 to 4.00)	4.00 (4.00 to 4.00)	4.00 (4.00 to 4.00)	4.00 (4.00 to 4.00)
carboxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	6.00 (4.00 to 8.00)	4.00 (3.00 to 8.00)	4.00 (3.00 to 8.00)	4.00 (3.00 to 4.00)
desmethyl-dabrafenib @ Wk1D1 (n=2,10,6,6,21,27)	4.00 (4.00 to 4.00)	4.00 (4.00 to 4.00)	4.00 (4.00 to 4.00)	4.00 (4.00 to 4.00)
desmethyl-dabrafenib @ Wk3D15 (n=3,10,8,6,24,29)	2.00 (0.00 to 8.00)	2.00 (0.50 to 8.00)	1.50 (0.00 to 8.00)	1.50 (0.00 to 3.00)

End point values	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	31		
Units: Hour (hr)				
median (full range (min-max))				
dabrafenib @ Wk1D1 (n=2,10,8,6,27,31)	2.00 (0.50 to 4.00)	2.00 (0.50 to 4.00)		
dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	2.00 (1.00 to 6.00)	2.00 (1.00 to 4.00)		
hydroxy-dabrafenib @ Wk1D1 (n=2,10,8,6,26,31)	4.00 (2.00 to 4.00)	4.00 (2.00 to 4.00)		
hydroxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	2.00 (1.00 to 6.00)	2.00 (1.00 to 4.00)		
carboxy-dabrafenib @ Wk1D1 (n=2,10,7,6,27,31)	4.00 (0.50 to 4.00)	4.00 (4.00 to 4.00)		
carboxy-dabrafenib @ Wk3D15 (n=3,10,8,6,26,29)	4.00 (0.00 to 8.00)	4.00 (2.00 to 8.00)		
desmethyl-dabrafenib @ Wk1D1 (n=2,10,6,6,21,27)	4.00 (0.50 to 4.00)	4.00 (4.00 to 4.00)		
desmethyl-dabrafenib @ Wk3D15 (n=3,10,8,6,24,29)	2.00 (0.00 to 8.00)	1.00 (0.00 to 8.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half life (T½) of dabrafenib and its metabolites

End point title	Elimination half life (T½) of dabrafenib and its metabolites[29]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. T1/2 of dabrafenib and its metabolites (hydroxy-dabrafenib [GSK2285403], carboxy-dabrafenib [GSK2298683], and desmethyl-dabrafenib [GSK2167542]) was listed and summarized using descriptive statistics.

End point type	Secondary

End point timeframe:

Week 3 Day 15

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Part 1

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	10	8	6
Units: Hour (hr)				
arithmetic mean (standard deviation)				
dabrafenib (n=3,10,8,6,25,29)	1.98 (± 0.687)	2.85 (± 1.58)	2.74 (± 0.840)	1.56 (± 0.359)
hydroxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
carboxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
desmethyl-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

End point values	Part 2 (Tumor Specific Expansion): All patients (4.5 mg/kg)	Part 2 (Tumor Specific Expansion): All patients (5.25 mg/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	31		
Units: Hour (hr)				
arithmetic mean (standard deviation)				
dabrafenib (n=3,10,8,6,25,29)	3.03 (± 2.27)	2.54 (± 2.44)		
hydroxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)		
carboxy-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)		
desmethyl-dabrafenib (n=0,0,0,0,0,0)	999 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment emergent Adverse Events (AEs) in Part 2 (Tumor Specific Expansion)

End point title	Incidence of treatment emergent Adverse Events (AEs) in Part 2 (Tumor Specific Expansion)[30]

End point description:

The distribution of adverse events will be done via the analysis of frequencies for treatment emergent Adverse Events, Serious Adverse Event and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters.

End point type	Secondary

End point timeframe:

From study treatment start date till 30 days safety follow-up, assessed up to approximately 90 months

Notes:

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

End point values	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)	Part 2 (Tumor specific expansion): Cohort 3 (LCH)	Part 2 (Tumor specific expansion): Cohort 4 (Other)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	28	11	2
Units: Participants				
All deaths (All grades)	0	1	0	0
All deaths (Grades 3/4/5)	0	1	0	0
On-treatment deaths (All grades)	0	0	0	0
On-treatment deaths (Grades 3/4/5)	0	0	0	0
Adverse Events (AEs) (All grades)	17	26	11	2
Adverse Events (AEs) (Grades 3/4/5)	10	13	9	2
AEs suspected to be drug related (All grades)	16	26	11	0
AEs suspected to be drug related (Grades 3/4/5)	4	5	2	0
Serious Adverse Events (SAEs) (All grades)	7	13	6	0
Serious Adverse Events (SAEs) (Grades 3/4/5)	5	8	3	0
SAEs suspected to be drug related (All grades)	1	3	2	0
SAEs suspected to be drug related (Grades 3/4/5)	0	1	0	0
Fatal SAEs (All grades)	0	1	0	0
Fatal SAEs (Grades 3/4/5)	0	1	0	0
AEs leading to discontinuation (All grades)	2	1	1	0
AEs leading to discontinuation (Grades 3/4/5)	0	1	0	0
AEs requiring dose interruptions (All grades)	10	13	7	2
AEs requiring dose interruptions (Grades 3/4/5)	3	6	3	1
AEs requiring dose reductions (All grades)	2	4	2	1
AEs requiring dose reductions (Grades 3/4/5)	1	0	0	1

End point values	Part 2 (Tumor Specific Expansion): All patients			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: Participants				
All deaths (All grades)	1			
All deaths (Grades 3/4/5)	1			
On-treatment deaths (All grades)	0			
On-treatment deaths (Grades 3/4/5)	0			
Adverse Events (AEs) (All grades)	56			
Adverse Events (AEs) (Grades 3/4/5)	34			
AEs suspected to be drug related (All grades)	53			
AEs suspected to be drug related (Grades 3/4/5)	11			
Serious Adverse Events (SAEs) (All grades)	26			
Serious Adverse Events (SAEs) (Grades 3/4/5)	16			
SAEs suspected to be drug related (All grades)	6			
SAEs suspected to be drug related (Grades 3/4/5)	1			
Fatal SAEs (All grades)	1			
Fatal SAEs (Grades 3/4/5)	1			
AEs leading to discontinuation (All grades)	4			
AEs leading to discontinuation (Grades 3/4/5)	1			
AEs requiring dose interruptions (All grades)	32			
AEs requiring dose interruptions (Grades 3/4/5)	13			
AEs requiring dose reductions (All grades)	9			
AEs requiring dose reductions (Grades 3/4/5)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response based on investigator assessment per Response Assessment in Neuro-Oncology (RANO) criteria for Low Grade Glioma (LLG) subjects

End point title	Best overall response based on investigator assessment per Response Assessment in Neuro-Oncology (RANO) criteria for Low Grade Glioma (LLG) subjects[31]

End point description:

Overall Response Rate (ORR) was defined as the proportion of participants with Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR).based on Response Assessment in Neuro-Oncology (RANO) criteria for Low Grade Glioma (LLG) and High Grade Glioma (HGG) subjects.

End point type	Secondary

End point timeframe:

Up to 6 months

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable to Low Grade Glioma (LLG) and High Grade Glioma (HGG) subjects

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	6	17
Units: Participants	3	5	4	12

End point values	All LGG subjects at Recommended Phase 2 dose (RP2D)	All LGG subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	33		
Units: Participants	17	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response based on investigator assessment per Response Assessment in Neuro-Oncology (RANO) criteria for High Grade Glioma (HGG) subjects

End point title	Best overall response based on investigator assessment per Response Assessment in Neuro-Oncology (RANO) criteria for High Grade Glioma (HGG) subjects[32]

End point description:

Overall Response Rate (ORR) was defined as the proportion of participants with Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR).based on Response Assessment in Neuro-Oncology (RANO) criteria for Low Grade Glioma (LLG) and High Grade Glioma (HGG) subjects.

End point type	Secondary

End point timeframe:

Up to 6 months

Notes:

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

Justification: Only applicable to Low Grade Glioma (LLG) and High Grade Glioma (HGG) subjects

End point values	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)	All HGG subjects at Recommended Phase 2 dose (RP2D)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	4	28	28
Units: Participants	2	1	7	7

End point values	All HGG subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Participants	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of age and weight on CL/F of dabrafenib

End point title	Effect of age and weight on CL/F of dabrafenib

End point description:

The CL/F data with the effect of age and weight using a population pharmacokinetic approach was to be evaluated.
The effect of age was not incorporated in the PopPK model, as body weight and age are correlated, and body-weight is a more informative to be used.

End point type	Secondary

End point timeframe:

Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.

End point values	All enrolled participants			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: No unit of measure				
number (not applicable)	0.223			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of age and weight on volume of distribution (V/F) of dabrafenib

End point title	Effect of age and weight on volume of distribution (V/F) of dabrafenib

End point description:

The V/F data with the effect of age and weight using a population pharmacokinetic approach was to be evaluated.
The effect of age was not incorporated in the PopPK model, as body weight and age are correlated, and body-weight is a more informative to be used.

End point type	Secondary

End point timeframe:

Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.

End point values	All enrolled participants			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: No unit of measure				
number (not applicable)	0.593			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of age and weight on absorption rate (ka) of dabrafenib

End point title	Effect of age and weight on absorption rate (ka) of dabrafenib

End point description:

The ka data with the effect of age and weight using a population pharmacokinetic approach was to be evaluated.
The effect of age was not incorporated in the PopPK model, as body weight and age are correlated, and body-weight is a more informative to be used.

End point type	Secondary

End point timeframe:

Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.

End point values	All enrolled participants			
Subject group type	Subject analysis set			
Number of subjects analysed	85[33]			
Units: No unit of measure	999			

Notes:

[33] - No covariate on KA parameter analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of age and weight on coefficients for significant covariates of dabrafenib

End point title	Effect of age and weight on coefficients for significant covariates of dabrafenib

End point description:

The coefficients for significant covariates data with the effect of age and weight using a population pharmacokinetic approach was to be evaluated.
The effect of age was not incorporated in the PopPK model, as body weight and age are correlated, and body-weight is a more informative to be used.

End point type	Secondary

End point timeframe:

Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.

End point values	All enrolled participants			
Subject group type	Subject analysis set			
Number of subjects analysed	85[34]			
Units: No unit of measure	999			

Notes:

[34] - No coefficients for significant covariates of dabrafenib

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment up to 28 days after the last dose, assessed up to approximately 90 months

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)

Reporting group description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)

Reporting group description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)

Reporting group description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)

Reporting group description:

Repeat dose, dose escalation study in patients with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). The starting dose was 3 mg/kg with subsequent dose levels: 3.75 mg/kg, 4.5 mg/kg, 5.25 mg/kg and 6.0 mg/kg.

Reporting group title	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)

Reporting group description:

Subjects with high-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Reporting group title	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)

Reporting group description:

Subjects with low-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Reporting group title	Part 2 (Tumor expansion): Cohort 3 (LCH)

Reporting group description:

Subjects with Langerhans cell histiocytosis (LCH) with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will

begin from Day 2, twice daily till end of study.

Reporting group title	Part 2 (Tumor expansion): Cohort 4 Miscellaneous tumors

Reporting group description:

Subjects with other tumors with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.

Serious adverse events	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	5 / 10 (50.00%)	5 / 8 (62.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Epstein-Barr virus associated lymphoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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 physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	6 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood culture positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Ejection fraction decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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			
Accidental overdose			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Overdose			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Shunt malfunction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Stroke-like migraine attacks after radiation therapy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Intracranial pressure increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Meningeal disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Blood and lymphatic system disorders			

Disseminated intravascular coagulation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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 and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Pityriasis rosea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Corynebacterium infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Croup infectious			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Herpes zoster			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Pharyngitis streptococcal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal bacteraemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Salmonellosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Staphylococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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
Varicella			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Hypophagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (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

Serious adverse events	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	7 / 17 (41.18%)	13 / 28 (46.43%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Epstein-Barr virus associated lymphoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Metastases to meninges			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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			
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	4 / 28 (14.29%)
occurrences causally related to treatment / all	0 / 2	0 / 2	2 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Product issues			
Device occlusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Investigations			
Blood culture positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Overdose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Shunt malfunction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (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
Stroke-like migraine attacks after radiation therapy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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			
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Depressed level of consciousness			

subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	3 / 28 (10.71%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (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
Meningeal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Seizure			

subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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			
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Pityriasis rosea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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

Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Corynebacterium infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Croup infectious			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (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
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (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
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Pharyngitis streptococcal			

subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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 tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Salmonellosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (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
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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
Hypophagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (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	Part 2 (Tumor expansion): Cohort 3 (LCH)	Part 2 (Tumor expansion): Cohort 4 Miscellaneous tumors	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 11 (54.55%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Epstein-Barr virus associated lymphoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (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			
Disease progression			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 11 (45.45%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	2 / 16	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood culture positive			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke-like migraine attacks after radiation therapy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (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			
Ataxia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningeal disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (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	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pityriasis rosea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (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			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (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			
Appendicitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corynebacterium infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (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	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (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	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	10 / 10 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	2	8	12
Skin papilloma			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	2	4	0
Acrochordon			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lip neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neoplasm skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Xanthogranuloma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	6	2
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	2	2	4
Haematoma			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Venous thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Surgical and medical procedures			
Steroid therapy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Chills			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	2	4	4
Complication associated with device			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	4
Face oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)	6 / 10 (60.00%)	2 / 8 (25.00%)
occurrences (all)	4	26	4
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	6	2
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	4	4
Pain			

subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	2	2	2
Pyrexia			
subjects affected / exposed	3 / 3 (100.00%)	5 / 10 (50.00%)	7 / 8 (87.50%)
occurrences (all)	12	50	40
Xerosis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	2	2	2
Catheter site erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Catheter site extravasation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Facial pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Feeling hot			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Localised oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	4
Drug hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Dysmenorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Testicular pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	5 / 10 (50.00%)	4 / 8 (50.00%)
occurrences (all)	28	16	12
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	4
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	12	10	14
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)	3 / 10 (30.00%)	1 / 8 (12.50%)
occurrences (all)	2	14	2
Rhinitis allergic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	6
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	4
Wheezing			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Adenoidal hypertrophy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Catarrh			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hypocapnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory acidosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Restrictive pulmonary disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Sleep apnoea syndrome			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Sneezing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	4
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	0	4	4
Depression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Mood altered			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	2
Affect lability			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Aggression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Anger			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2

Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysphemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Emotional disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Hallucination			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Irritability			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Middle insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	4 / 10 (40.00%)	2 / 8 (25.00%)
occurrences (all)	2	22	4
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	3 / 8 (37.50%)
occurrences (all)	2	8	6
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Blood creatinine decreased			

subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	8
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Haemoglobin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	6
Lymphocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	2	12	4
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	16	0	4
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	3 / 8 (37.50%)
occurrences (all)	10	4	6
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	4
Weight increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	8
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	10	2	0
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood calcium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood chloride increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood fibrinogen decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood luteinising hormone increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Blood prolactin abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood urea decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	4
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Carbon dioxide decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Cardiac murmur			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Creatinine urine decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eosinophil count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Platelet count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Protein total increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Red blood cell count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory rate decreased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Urine analysis abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	0	6	6
Contusion			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Fall			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	3 / 8 (37.50%)
occurrences (all)	2	0	6
Gastrostomy tube site complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Procedural pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	4	4
Animal bite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Animal scratch			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Clavicle fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Foot fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hand fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nail avulsion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Overdose			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Radius fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Scar			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Skin abrasion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Sunburn			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Upper limb fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Wound			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	6	2	0
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	8
Bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Cardiac disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mitral valve incompetence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Sinus bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tricuspid valve disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	3 / 10 (30.00%)	2 / 8 (25.00%)
occurrences (all)	6	10	16
Headache			
subjects affected / exposed	1 / 3 (33.33%)	8 / 10 (80.00%)	3 / 8 (37.50%)
occurrences (all)	20	34	28
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	4
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Altered state of consciousness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Ataxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Dysaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Dysarthria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Dysmetria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Facial nerve disorder			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hemianopia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Hypersomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Muscle spasticity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Nystagmus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oculofacial paralysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Partial seizures			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Periodic limb movement disorder			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Psychomotor hyperactivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
VIth nerve paralysis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Visual field defect			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	6	6	4
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	4
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	4
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Monocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Neutrophilia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thrombocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	8	2	0
Cerumen impaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Deafness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Excessive cerumen production			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
External ear inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Eye pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blepharospasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dark circles under eyes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry eye			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Hypermetropia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Myopia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Ocular hyperaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Optic nerve disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Papilloedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Periorbital swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Retinal exudates			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Scleral disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Uveitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Vernal keratoconjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Visual acuity reduced			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	4 / 10 (40.00%)	1 / 8 (12.50%)
occurrences (all)	4	10	2
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	2	10	10
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	3 / 8 (37.50%)
occurrences (all)	2	2	18
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	4 / 8 (50.00%)
occurrences (all)	0	4	16
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	5 / 10 (50.00%)	2 / 8 (25.00%)
occurrences (all)	4	14	16
Oral disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Oral pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	5 / 10 (50.00%)	5 / 8 (62.50%)
occurrences (all)	10	30	22
Angular cheilitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chapped lips			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Cheilitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Cheilosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Dental caries			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Duodenitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Gastrointestinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2

Glossodynia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Odynophagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Oral mucosal eruption			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Paraesthesia oral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tongue ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	4	2
Alopecia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 10 (30.00%)	0 / 8 (0.00%)
occurrences (all)	2	8	0
Blister			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	6	2
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Dry skin			
subjects affected / exposed	1 / 3 (33.33%)	6 / 10 (60.00%)	3 / 8 (37.50%)
occurrences (all)	2	14	8
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	4	2
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	0	18	4
Erythema nodosum			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	6
Hyperkeratosis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	3 / 8 (37.50%)
occurrences (all)	0	14	6
Keratosis pilaris			
subjects affected / exposed	1 / 3 (33.33%)	3 / 10 (30.00%)	3 / 8 (37.50%)
occurrences (all)	2	6	10
Macule			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	4
Pain of skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Palmar-plantar erythrodysaesthesia			

syndrome			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Palmoplantar keratoderma			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Panniculitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	2
Papule			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	2 / 8 (25.00%)
occurrences (all)	0	6	6
Rash			
subjects affected / exposed	1 / 3 (33.33%)	4 / 10 (40.00%)	2 / 8 (25.00%)
occurrences (all)	2	22	8
Rash macular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)	3 / 10 (30.00%)	3 / 8 (37.50%)
occurrences (all)	10	6	10
Rash papular			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	4 / 8 (50.00%)
occurrences (all)	2	2	14
Rash pruritic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Skin discolouration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2

Skin disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	2 / 8 (25.00%)
occurrences (all)	0	8	8
Skin hyperpigmentation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	4	4
Skin hypertrophy			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	2 / 8 (25.00%)
occurrences (all)	0	8	6
Skin mass			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Yellow skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Cafe au lait spots			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Dermal cyst			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dermatitis bullous			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0

Dermatitis contact			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	4
Ecchymosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eczema asteatotic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Ephelides			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hair colour changes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hidradenitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Ingrown hair			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Intertrigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Keloid scar			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lentigo			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0

Miliaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Nail discolouration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Nail disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nail pigmentation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neurodermatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Onychomadesis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Photosensitivity reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash vesicular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Scab			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Seborrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Skin fissures			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Skin induration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Skin odour abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Xeroderma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Proteinuria			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	4 / 8 (50.00%)
occurrences (all)	2	4	8
Haemoglobinuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Microalbuminuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Polyuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal tubular disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			

subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Urinary tract pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Adrenal insufficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Precocious puberty			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 10 (40.00%)	2 / 8 (25.00%)
occurrences (all)	2	14	10
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	1 / 8 (12.50%)
occurrences (all)	0	6	4
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	0 / 8 (0.00%)
occurrences (all)	0	8	0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	6	2
Neck pain			

subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	0 / 8 (0.00%)
occurrences (all)	0	8	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	4 / 10 (40.00%)	2 / 8 (25.00%)
occurrences (all)	0	24	14
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ligament pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Limb mass			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Muscle contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal deformity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	4	2	0
Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Ear infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	8

Folliculitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	1 / 8 (12.50%)
occurrences (all)	0	10	4
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Herpes zoster			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Influenza			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	2	4	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	3 / 8 (37.50%)
occurrences (all)	4	2	8
Parainfluenzae virus infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Pharyngitis			
subjects affected / exposed	2 / 3 (66.67%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	4	2	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Rash pustular			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	4
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2

Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	2 / 8 (25.00%)
occurrences (all)	0	4	4
Rhinovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	4	2
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	6
Tinea pedis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	2 / 10 (20.00%)	5 / 8 (62.50%)
occurrences (all)	14	8	20
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	4
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Carbuncle			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Coronavirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Croup infectious			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Enterobiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Enterovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Furuncle			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastritis viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Groin abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metapneumovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0

Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Paronychia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pertussis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Pitted keratolysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Skin bacterial infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0

Streptococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Tinea cruris			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Tinea infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Tonsillitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Tracheostomy infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Varicella			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vascular device infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Viral rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vulval abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	3 / 8 (37.50%)
occurrences (all)	0	6	6
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	4
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	14	2
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 10 (30.00%)	3 / 8 (37.50%)
occurrences (all)	2	16	10
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	1 / 8 (12.50%)
occurrences (all)	0	10	2
Hypermagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	2 / 8 (25.00%)
occurrences (all)	0	24	6
Hyperuricaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	2	2	4
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	12	0
Hyponatraemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	2 / 8 (25.00%)
occurrences (all)	0	2	6
Hypophosphataemia			
subjects affected / exposed	2 / 3 (66.67%)	3 / 10 (30.00%)	4 / 8 (50.00%)
occurrences (all)	4	6	10
Folate deficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hyperchloraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Iron deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Vitamin D deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	17 / 17 (100.00%)	26 / 28 (92.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	2 / 6 (33.33%)	3 / 17 (17.65%)	8 / 28 (28.57%)
occurrences (all)	4	14	22
Skin papilloma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	4
Acrochordon			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Lip neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Neoplasm skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Xanthogranuloma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	2	6	2
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)	2 / 17 (11.76%)	4 / 28 (14.29%)
occurrences (all)	4	6	10
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	10	0
Haematoma			

subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Venous thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Steroid therapy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	6 / 28 (21.43%)
occurrences (all)	2	0	12
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Complication associated with device			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Face oedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)	6 / 17 (35.29%)	11 / 28 (39.29%)
occurrences (all)	14	14	26
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Pain			

subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	2	2	2
Pyrexia			
subjects affected / exposed	5 / 6 (83.33%)	11 / 17 (64.71%)	10 / 28 (35.71%)
occurrences (all)	24	46	206
Xerosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Catheter site erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Catheter site extravasation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Facial pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Malaise			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Non-cardiac chest pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	4	2	0
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Peripheral swelling			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Testicular pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 6 (50.00%)	3 / 17 (17.65%)	8 / 28 (28.57%)
occurrences (all)	20	8	22
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	3 / 17 (17.65%)	1 / 28 (3.57%)
occurrences (all)	2	6	4
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	6	6	2
Oropharyngeal pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	6	0	2
Rhinitis allergic			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Rhinorrhoea			
subjects affected / exposed	3 / 6 (50.00%)	3 / 17 (17.65%)	4 / 28 (14.29%)
occurrences (all)	12	6	8
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Adenoidal hypertrophy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Catarrh			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypocapnia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Laryngeal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Respiratory acidosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Restrictive pulmonary disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			

subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Tachypnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	8	2	2
Depression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	6	0	0
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Mood altered			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Affect lability			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Aggression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Anger			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0

Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dysphemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Emotional disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	4	2	0
Middle insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	3 / 17 (17.65%)	0 / 28 (0.00%)
occurrences (all)	8	16	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	8	0	4
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	4	2	2
Blood creatinine decreased			

subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Blood creatinine increased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 17 (17.65%)	5 / 28 (17.86%)
occurrences (all)	6	6	18
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	2 / 28 (7.14%)
occurrences (all)	2	2	6
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Haemoglobin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 17 (17.65%)	2 / 28 (7.14%)
occurrences (all)	4	16	4
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	4	0
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	4	2	2
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	2 / 28 (7.14%)
occurrences (all)	2	2	4
Weight increased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 17 (17.65%)	1 / 28 (3.57%)
occurrences (all)	4	8	2
White blood cell count decreased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	2 / 28 (7.14%)
occurrences (all)	2	8	4
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Blood bilirubin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood calcium decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Blood chloride increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	4
Blood fibrinogen decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Blood luteinising hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood prolactin abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Blood urea decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Carbon dioxide decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Creatinine urine decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Eosinophil count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Platelet count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Protein total increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	6	0
Protein urine present			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	6	0
Red blood cell count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Respiratory rate decreased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	4	2	0
Contusion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	8	2	0
Fall			
subjects affected / exposed	2 / 6 (33.33%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	4	2	0
Gastrostomy tube site complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Animal bite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Animal scratch			

subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Clavicle fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Hand fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Nail avulsion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Overdose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Scar			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Skin laceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sunburn			

subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Upper limb fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	4	2	4
Bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Cardiac disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Mitral valve incompetence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Tricuspid valve disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	2 / 28 (7.14%)
occurrences (all)	2	6	4
Headache			
subjects affected / exposed	2 / 6 (33.33%)	8 / 17 (47.06%)	10 / 28 (35.71%)
occurrences (all)	22	36	28
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	0	4	2
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	4 / 28 (14.29%)
occurrences (all)	0	0	12
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	4
Altered state of consciousness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Dysaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Dysmetria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Facial nerve disorder			

subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Hemianopia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypersomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	4
Lethargy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Migraine			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Muscle spasticity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Nervous system disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nystagmus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Oculofacial paralysis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Partial seizures			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Periodic limb movement disorder			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
VIth nerve paralysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 6 (50.00%)	5 / 17 (29.41%)	4 / 28 (14.29%)
occurrences (all)	8	18	10
Leukocytosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	4	0	2
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	4
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	3 / 28 (10.71%)
occurrences (all)	2	0	16
Thrombocytopenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	2	2	2
Monocytosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Neutrophilia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Thrombocytosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Cerumen impaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Deafness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Excessive cerumen production			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
External ear inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Eye pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	4	0
Blepharospasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Dark circles under eyes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Dry eye			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	6
Eye pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypermetropia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Myopia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Optic nerve disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Papilloedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Periorbital swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Retinal exudates			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Scleral disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Uveitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vernal keratoconjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	4 / 17 (23.53%)	3 / 28 (10.71%)
occurrences (all)	26	14	10
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	4	0	2
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	4
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)	6 / 17 (35.29%)	4 / 28 (14.29%)
occurrences (all)	16	24	8
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	4
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	2 / 17 (11.76%)	7 / 28 (25.00%)
occurrences (all)	18	6	16
Oral disorder			
subjects affected / exposed	2 / 6 (33.33%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	4	4	0

Oral pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	4 / 6 (66.67%)	6 / 17 (35.29%)	10 / 28 (35.71%)
occurrences (all)	40	34	34
Angular cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Chapped lips			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cheilosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Chronic gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Duodenitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Glossodynia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	6
Oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Oral mucosal eruption			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	4	2	0
Tongue ulceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	2 / 28 (7.14%)
occurrences (all)	0	2	6
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	3 / 28 (10.71%)
occurrences (all)	0	6	6
Blister			

subjects affected / exposed	0 / 6 (0.00%)	4 / 17 (23.53%)	1 / 28 (3.57%)
occurrences (all)	0	10	2
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	4 / 17 (23.53%)	0 / 28 (0.00%)
occurrences (all)	0	8	0
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Dry skin			
subjects affected / exposed	4 / 6 (66.67%)	7 / 17 (41.18%)	9 / 28 (32.14%)
occurrences (all)	16	20	18
Eczema			
subjects affected / exposed	2 / 6 (33.33%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	4	10	2
Erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	8
Erythema nodosum			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	4	2
Hair texture abnormal			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	2	4	2
Hyperkeratosis			
subjects affected / exposed	2 / 6 (33.33%)	4 / 17 (23.53%)	4 / 28 (14.29%)
occurrences (all)	4	14	8
Keratosis pilaris			
subjects affected / exposed	2 / 6 (33.33%)	0 / 17 (0.00%)	4 / 28 (14.29%)
occurrences (all)	4	0	8
Macule			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Pain of skin			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	0	6	2
Palmar-plantar erythrodysaesthesia			

syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Palmoplantar keratoderma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Panniculitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	0	10	2
Papule			
subjects affected / exposed	2 / 6 (33.33%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	4	0	2
Pruritus			
subjects affected / exposed	2 / 6 (33.33%)	5 / 17 (29.41%)	1 / 28 (3.57%)
occurrences (all)	4	12	2
Rash			
subjects affected / exposed	3 / 6 (50.00%)	6 / 17 (35.29%)	8 / 28 (28.57%)
occurrences (all)	8	22	22
Rash macular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	5 / 17 (29.41%)	3 / 28 (10.71%)
occurrences (all)	2	20	6
Rash papular			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Rash pruritic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Skin discolouration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Skin disorder			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	0	4	2
Skin exfoliation			
subjects affected / exposed	1 / 6 (16.67%)	3 / 17 (17.65%)	0 / 28 (0.00%)
occurrences (all)	2	6	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 6 (16.67%)	4 / 17 (23.53%)	1 / 28 (3.57%)
occurrences (all)	2	10	4
Skin hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	3 / 6 (50.00%)	3 / 17 (17.65%)	1 / 28 (3.57%)
occurrences (all)	8	6	2
Skin mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Yellow skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Cafe au lait spots			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Dermatitis bullous			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Dermatitis contact			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Eczema asteatotic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ephelides			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Hair colour changes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hidradenitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ingrown hair			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Intertrigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Keloid scar			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Lentigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0

Miliaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nail discolouration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nail pigmentation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Neurodermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Onychomadesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Rash erythematous			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Rash vesicular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Seborrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Skin fissures			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin induration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Skin odour abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Xeroderma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Proteinuria			
subjects affected / exposed	1 / 6 (16.67%)	3 / 17 (17.65%)	4 / 28 (14.29%)
occurrences (all)	8	14	20
Haemoglobinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Microalbuminuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Renal tubular disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	2 / 28 (7.14%)
occurrences (all)	2	12	4
Adrenal insufficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Precocious puberty			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 6 (33.33%)	4 / 17 (23.53%)	4 / 28 (14.29%)
occurrences (all)	4	16	14
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	3 / 28 (10.71%)
occurrences (all)	2	2	6
Muscle spasms			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	2	12	2
Muscular weakness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	4	0
Neck pain			

subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Pain in extremity			
subjects affected / exposed	2 / 6 (33.33%)	3 / 17 (17.65%)	4 / 28 (14.29%)
occurrences (all)	4	12	10
Flank pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Ligament pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Limb mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Muscle contracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal deformity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Musculoskeletal stiffness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	4
Ear infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	2	2	2

Folliculitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	2
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	2 / 28 (7.14%)
occurrences (all)	2	6	4
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	3 / 28 (10.71%)
occurrences (all)	2	4	10
Otitis media			
subjects affected / exposed	2 / 6 (33.33%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	4	2	2
Parainfluenzae virus infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	8	0	8
Pharyngitis streptococcal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Rash pustular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Rhinitis			
subjects affected / exposed	2 / 6 (33.33%)	2 / 17 (11.76%)	4 / 28 (14.29%)
occurrences (all)	4	4	14
Rhinovirus infection			
subjects affected / exposed	2 / 6 (33.33%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	6	2	0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	3 / 28 (10.71%)
occurrences (all)	0	16	10
Tinea pedis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	0 / 17 (0.00%)	4 / 28 (14.29%)
occurrences (all)	4	0	12
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	4 / 17 (23.53%)	0 / 28 (0.00%)
occurrences (all)	2	8	0
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	0	4	2
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Carbuncle			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Coronavirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Croup infectious			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0

Enterobiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Enterovirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Eye infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Furuncle			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Gastritis viral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Groin abscess			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Impetigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Metapneumovirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	4	0	4
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Otitis externa			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Otitis media acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Paronychia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Pertussis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pitted keratolysis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Pustule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Skin bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Streptococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tinea cruris			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tinea infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tracheostomy infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Viral rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vulval abscess			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	4 / 6 (66.67%)	1 / 17 (5.88%)	6 / 28 (21.43%)
occurrences (all)	12	2	12
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	8	0
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 17 (17.65%)	3 / 28 (10.71%)
occurrences (all)	2	12	6
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Hypermagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	0	4	2
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 17 (17.65%)	1 / 28 (3.57%)
occurrences (all)	0	12	2
Hyperuricaemia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	10	4	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	2	2	0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 28 (0.00%)
occurrences (all)	0	6	0
Hypokalaemia			
subjects affected / exposed	3 / 6 (50.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	10	2	2
Hypomagnesaemia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 17 (11.76%)	1 / 28 (3.57%)
occurrences (all)	8	16	2
Hyponatraemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	3 / 6 (50.00%)	3 / 17 (17.65%)	4 / 28 (14.29%)
occurrences (all)	10	6	8
Folate deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hyperchloraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Iron deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	4
Metabolic acidosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
Polydipsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2

Non-serious adverse events	Part 2 (Tumor expansion): Cohort 3 (LCH)	Part 2 (Tumor expansion): Cohort 4 Miscellaneous tumors	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	2 / 2 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)	
occurrences (all)	18	0	
Skin papilloma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Acrochordon			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Lip neoplasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Neoplasm skin			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Xanthogranuloma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Haematoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Hot flush			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Venous thrombosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Surgical and medical procedures			
Steroid therapy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Complication associated with device			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Face oedema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	12	0	
Gait disturbance			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Influenza like illness			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pyrexia			

subjects affected / exposed	4 / 11 (36.36%)	2 / 2 (100.00%)	
occurrences (all)	20	4	
Xerosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Catheter site erythema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Catheter site extravasation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Chest pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Facial pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Feeling hot			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Localised oedema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Drug hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dysmenorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Testicular pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 11 (54.55%)	0 / 2 (0.00%)	
occurrences (all)	34	0	
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	10	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Rhinitis allergic			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Rhinorrhoea			

subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Wheezing			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Adenoidal hypertrophy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Catarrh			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypocapnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Laryngeal inflammation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Productive cough			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory acidosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory tract congestion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Restrictive pulmonary disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Sneezing			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tachypnoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Anxiety			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Depression			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Mood altered			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Affect lability			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Aggression			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Anger			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Attention deficit hyperactivity disorder			

subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Dysphemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Emotional disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hallucination			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Irritability			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Middle insomnia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Suicidal ideation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	10	0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Blood alkaline phosphatase decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Blood creatinine decreased			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Blood creatinine increased				
subjects affected / exposed	5 / 11 (45.45%)	0 / 2 (0.00%)		
occurrences (all)	26	0		
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)		
occurrences (all)	2	0		
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)		
occurrences (all)	2	0		
Haemoglobin increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Lymphocyte count decreased				
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)		
occurrences (all)	2	0		
Neutrophil count decreased				
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)		
occurrences (all)	16	0		
Platelet count decreased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Weight decreased				
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)		
occurrences (all)	4	0		
Weight increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
White blood cell count decreased				
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)		
occurrences (all)	26	0		
Activated partial thromboplastin time prolonged				

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood albumin decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood bilirubin decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood bilirubin increased			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Blood calcium decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood chloride increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood fibrinogen decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood luteinising hormone increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood prolactin abnormal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood urea decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

Carbon dioxide decreased				
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)		
occurrences (all)	4	0		
Cardiac murmur				
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)		
occurrences (all)	2	0		
Creatinine urine decreased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Ejection fraction decreased				
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)		
occurrences (all)	2	0		
Eosinophil count increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
International normalised ratio increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Low density lipoprotein increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Platelet count increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Protein total increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Protein urine present				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Red blood cell count increased				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Respiratory rate decreased				

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Transaminases increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	2	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Urine analysis abnormal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Contusion			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Fall			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Gastrostomy tube site complication			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Animal bite			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Animal scratch			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Clavicle fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Foot fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hand fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Ligament sprain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nail avulsion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Overdose			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Radius fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Scar			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin abrasion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin laceration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Sunburn			

subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Upper limb fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Wound			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	12	0	
Tachycardia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Bradycardia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cardiac disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Mitral valve incompetence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Palpitations			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Sinus bradycardia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Tricuspid valve disease			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Dizziness				
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)		
occurrences (all)	4	0		
Headache				
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)		
occurrences (all)	12	0		
Paraesthesia				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Seizure				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Somnolence				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Syncope				
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)		
occurrences (all)	4	0		
Altered state of consciousness				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Ataxia				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Dysaesthesia				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Dysarthria				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Dysmetria				
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)		
occurrences (all)	0	0		
Facial nerve disorder				

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hemianopia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypersomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Lethargy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Migraine			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Muscle spasticity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nervous system disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nystagmus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oculofacial paralysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Partial seizures			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Periodic limb movement disorder			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Tremor			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
VIth nerve paralysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Visual field defect			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Leukocytosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Leukopenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Lymphopenia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Thrombocytopenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Monocytosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	8	0	

Neutrophilia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Thrombocytosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Cerumen impaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Deafness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Excessive cerumen production			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
External ear inflammation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Eye pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Blepharospasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dark circles under eyes			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dry eye			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Eye pruritus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypermetropia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Keratitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Myopia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Ocular hyperaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Optic nerve disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Papilloedema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Periorbital swelling			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Photophobia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Retinal exudates			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Scleral disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Uveitis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vernal keratoconjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Visual acuity reduced			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)	
occurrences (all)	12	0	
Diarrhoea			
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)	
occurrences (all)	20	0	
Dyspepsia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)	
occurrences (all)	16	0	
Oral disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Oral pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Toothache			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	9 / 11 (81.82%)	0 / 2 (0.00%)	
occurrences (all)	40	0	
Angular cheilitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Chapped lips			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cheilitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cheilosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Chronic gastritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dental caries			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Duodenal ulcer			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Duodenitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Glossodynia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Mouth ulceration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Odynophagia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oesophagitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oral mucosal eruption			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Paraesthesia oral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tongue ulceration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Alopecia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Blister			

subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Dermatitis acneiform			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	5 / 11 (45.45%)	0 / 2 (0.00%)	
occurrences (all)	16	0	
Eczema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Erythema			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Erythema nodosum			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Hair texture abnormal			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Hyperkeratosis			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	10	0	
Keratosis pilaris			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Macule			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Pain of skin			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Palmar-plantar erythrodysaesthesia			

syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Palmoplantar keratoderma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Panniculitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Papule			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Rash macular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Rash papular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Rash pruritic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Skin discolouration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

Skin disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin exfoliation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Skin hyperpigmentation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Skin hypertrophy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin lesion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Skin mass			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Yellow skin			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cafe au lait spots			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dermal cyst			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dermatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dermatitis bullous			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

Dermatitis contact			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Dermatitis diaper			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Ecchymosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Eczema asteatotic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Ephelides			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hair colour changes			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Hidradenitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hyperhidrosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Ingrown hair			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Intertrigo			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Keloid scar			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Lentigo			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Miliaria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nail discolouration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nail disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Nail pigmentation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Neurodermatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Night sweats			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Onychomadesis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Photosensitivity reaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Rash erythematous			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Rash vesicular			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Scab			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Seborrhoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

Skin fissures			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin induration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin odour abnormal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Xeroderma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Haemoglobinuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Microalbuminuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Polyuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Renal tubular disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	2	
Urinary incontinence			

subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Urinary tract pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Adrenal insufficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Precocious puberty			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Neck pain			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	10	0	
Flank pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Ligament pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Limb mass			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Muscle contracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal deformity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis			
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)	
occurrences (all)	10	0	
Ear infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	2	

Folliculitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Rash pustular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Rhinitis			
subjects affected / exposed	3 / 11 (27.27%)	1 / 2 (50.00%)	
occurrences (all)	24	2	
Rhinovirus infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Tinea pedis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 11 (36.36%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Urinary tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
COVID-19			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Candida infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Carbuncle			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Coronavirus infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Croup infectious			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

Enterobiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Enterovirus infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Eye infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Fungal infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Fungal skin infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Furuncle			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastritis viral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Groin abscess			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Impetigo			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Metapneumovirus infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Onychomycosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Oral candidiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Otitis externa			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Otitis media acute			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Paronychia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pertussis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pitted keratolysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pustule			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin bacterial infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Staphylococcal infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Streptococcal infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tinea cruris			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tinea infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tonsillitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Tooth infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tracheostomy infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Varicella			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vascular device infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Viral rash			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Vulval abscess			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Hypercalcaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 2 (0.00%)	
occurrences (all)	12	0	
Hyperkalaemia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Hypermagnesaemia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Hypernatraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hyperuricaemia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Hypoalbuminaemia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Hypoglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Hypokalaemia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hyponatraemia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypophosphataemia			
subjects affected / exposed	5 / 11 (45.45%)	1 / 2 (50.00%)	
occurrences (all)	18	2	
Folate deficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hyperchloraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hyperlipidaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hyperphosphataemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Iron deficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Metabolic acidosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Polydipsia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vitamin D deficiency			
subjects affected / exposed	1 / 11 (9.09%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2012	1.0, 19-Oct-2012: Corrected Inclusion Criteria #6 to ensure consistency with the contraception requirements as outlined in Section 7.1.1; the requirement for male contraception was deleted since the risk of embryofetal developmental toxicity as a consequence of exposure to female pregnant partners is very low. In addition, the dose escalation procedure table provided in Appendix 1 was changed to ensure that escalation of dose when 6 subjects are enrolled occurs only if there are ≤1 subject with a DLT and no subject data pending, and to fix the reference and formatting
13 December 2012	2.0, 13-Dec-2012: Amendment No. 02 is a country-specific amendment for France which prohibits children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules from inclusion in the study in France (pending availability of an oral suspension formulation); changes the QTc stopping criteria to 500 msec for French subjects (as compared to 530 msec); adds cardiac monitoring by echocardiogram (ECHO) at Week 4; and highlights that ECHOs are to be performed by the same operator throughout the study, where possible.
28 March 2013	3.0, 28-Mar-2013: To take into account potential renal effects, Amendment 03 changed the lower age limit of inclusion criterion #2 from subjects 1 month old to ≥12 months old, adjusted criteria for adequate renal function in inclusion criterion #7, added guidelines for renal insufficiency and additional laboratory testing. Information on the new suspension formulation was incorporated. The section on dose modification was re-organized for consistency. The Time and Events Table was adjusted to include assessments on Day 22, Week 4 was clarified to be Day 29, and increased chemistry and urinalysis evaluations were added.
19 June 2013	4.0, 19-Jun-2013: Expanded eligibility to subjects with refractory disease, and allows for BID dosing on Day 1. Clarifications made to glioma scan requirements and BRAF mutation testing timing. Pyrexia management guidelines updated and Prohibited and Cautionary medication section updated.
25 July 2013	5.0, 25-Jul-2013: to clarify the dose escalation rules to allow selection of the appropriate dose by age group in the absence of MTD; to include 2 additional dose levels; to clarify that at least 5 subjects less than 6 years old will be enrolled to be consistent with the binding elements of the Pediatric Investigation Plan (PIP); to clarify the general dose modification guidelines; to clarify the DLT evaluable population and PK population; to update the T&E table to specify that ECHOs will be collected for all subjects; to correct Appendix 1.
30 July 2014	6.0, 30-Jul-2014: Title changed to specify children and adolescents instead of specific years. Lower age range increased to ≥12 months from >1 month. Study rationale updated to specify refractory disease. Clarification of the dose escalation rules for selection of the appropriate dose by age group in the absence of MTD. Addition of LCH assessments to the time and events schedule, and addition of the LCH scoring system. Overdose section updated in accordance with the most recent information available for dabrafenib. SAE definition of protocol-specific SAEs updated for clarity and modified based on additional understanding of the compound.
15 September 2016	7.0, 15-Sep-2016: References to GSK or its staff were deleted and replaced with those of Novartis/Novartis and its authorized agents. Administrative changes to align with Novartis processes and procedures were made.

19 May 2017	8.0, 19-May-2017: To allow the enrollment of additional subjects in the HGG cohort of Part 2 of the study. This cohort was originally planned to include approximately 10 subjects and has enrolled 21 subjects in Part 2 to date. In view of the promising efficacy in this otherwise very poor prognosis disease, enrollment will remain open until another pediatric HGG study is open for enrollment of this population across all age groups in the same countries (expected by the end of 2018 and no later than mid 2019). Enrollment into the LGG and LCH cohorts have not been extended as subjects may be able to enroll into another pediatric study (MEK116540). The data analysis and statistical consideration was updated to align the analysis populations with the statistical analysis plan. Two interim analyses were added to explain a past unplanned interim analysis and a future interim analysis for decision making of development options. Independent review of HGG tumor histology was clarified in the protocol. It has been shown that LGG can be misdiagnosed for HGG, so the independent review was to ensure consistent application of the WHO glioma classification scale to allow for more reliable comparison to historical studies. As a sensitivity analysis, the efficacy data was to be analyzed including only subjects with centrally confirmed HGG.
17 September 2018	9.0, 17-Sep-2018: The purpose of this amendment was: i) Addition of a new pediatric formulation dosage form of dabrafenib 10mg as dispersible tablets. ii) Update the withdrawal of consent language to align with the new Global Data Protection Requirements.
04 April 2019	10.0, 04-Apr-2019: The purpose of this amendment was to add additional interim analyses of data to support a regulatory submission
21 August 2020	11.0, 21-Aug-2020: The purpose of this amendment was to change the target subject enrollment number for the miscellaneous tumor cohort. The trial has enrolled only four subjects with miscellaneous tumor types (those that are BRAFV600 mutant but are not HGG, LGG, or LCH); two in the dose finding portion, two in the dedicated miscellaneous cohort, over the more than 5 years of enrollment. The miscellaneous cohort was not required for regulatory obligations, and was not required to meet the aims of the clinical trial. Hence, the proposed enrollment target for the miscellaneous cohort was modified from ‘at least 10 subjects’ to ‘up to ten subjects.’ The protocol was also amended to add updated RANO criteria specifically for low grade glioma (RANO-LGG; Wen 2017) as the basis for independent review.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: