



## 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	v2 (current)
This version publication date	26 December 2021
First version publication date	20 June 2021
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	116013
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##### 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	Novartis Campus, 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)	EMA-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
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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
<b>Arm title</b>	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.

<b>Arm title</b>	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)
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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	
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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.

<b>Arm title</b>	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
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**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.

<b>Arm title</b>	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)
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**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.

<b>Arm title</b>	Part 2 (Tumor specific expansion): Cohort 1 (LGG)
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**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
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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.

<b>Arm title</b>	Part 2 (Tumor specific expansion): Cohort 2 (HGG)
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**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.

<b>Arm title</b>	Part 2 (Tumor specific expansion): Cohort 3 (LCH)
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**Arm description:**

Subjects with 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.

<b>Arm title</b>	Part 2 (Tumor specific expansion): Cohort 4 (Other)
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**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
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 specific expansion): Cohort 1 (LGG)	Part 2 (Tumor specific expansion): Cohort 2 (HGG)
		Started	6
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)
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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)
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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)
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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)
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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 specific expansion): Cohort 1 (LGG)
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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 specific expansion): Cohort 2 (HGG)
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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)
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Reporting group description:

Subjects with 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)
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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

<b>Reporting group values</b>	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor specific expansion): Cohort 1 (LGG)	Part 2 (Tumor specific expansion): Cohort 2 (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 standard deviation	7.17 ± 3.189	9.65 ± 5.195	12.32 ± 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

<b>Reporting group values</b>	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 standard deviation	5.52 ± 3.390	9.50 ± 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

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## Subject analysis sets

Subject analysis set title	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients at recommended dose phase 2 (RP2D) of 4,5 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients at recommended dose phase 2 (RP2D) of 5.25 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients at recommended dose phase 2 (RP2D) of 4,5 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients at recommended dose phase 2 (RP2D) of 5.25 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients at recommended dose phase 2 (RP2D) of 4,5 mg/kg in Part 2 study cohorts (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 patients who have been assigned to Recommended Phase II Dose (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 in the study

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 patients who have been assigned to Recommended Phase II Dose (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 in the study

Subject analysis set title	Part 1 and Part 2 – All participants with PK data
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the study (all doses and all tumor types) with available pharmacokinetic data

<b>Reporting group values</b>	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg
Number of subjects	27	31	26
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			

<b>Reporting group values</b>	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg	All LGG subjects at Recommended Phase 2 dose (RP2D)
Number of subjects	29	25	24
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 ±
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			

<b>Reporting group values</b>	All LGG subjects	All HGG subjects at Recommended Phase 2 dose (RP2D)	All HGG subjects
Number of subjects	33	28	35
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	24 ±	7 ±	10 ±
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			

<b>Reporting group values</b>	Part 1 and Part 2 – All participants with PK data		
Number of subjects	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	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			

## 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 specific expansion): Cohort 1 (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 specific expansion): Cohort 2 (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 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 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients at recommended dose phase 2 (RP2D) of 4,5 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients at recommended dose phase 2 (RP2D) of 5.25 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients at recommended dose phase 2 (RP2D) of 4,5 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients at recommended dose phase 2 (RP2D) of 5.25 mg/kg in Part 2 study cohorts (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	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients at recommended dose phase 2 (RP2D) of 4,5 mg/kg in Part 2 study cohorts (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 patients who have been assigned to Recommended Phase II Dose (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 in the study	
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 patients who have been assigned to Recommended Phase II Dose (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 in the study	
Subject analysis set title	Part 1 and Part 2 – All participants with PK data
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants in the study (all doses and all tumor types) with available pharmacokinetic data	

**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) <sup>[1][2]</sup>
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End point description:

The distribution of adverse events was 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 28 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: Primary endpoint "Incidence of treatment emergent Adverse Events (AEs) in Part 1 (Dose Escalation)" only apply 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	0	0	0	1
On-treatment deaths	0	0	0	1
Adverse Events (AEs)	3	10	8	6
AEs suspected to be drug related	3	10	8	5
Serious Adverse Events (SAEs)	0	5	5	3
SAEs suspected to be drug related	0	2	2	1
Fatal SAEs	0	0	0	1
Fatal SAEs suspected to be drug related	0	0	0	0
AEs leading to discontinuation	0	0	1	0
AEs requiring dose interruptions	1	5	6	5
AEs requiring dose reductions	0	2	3	1
AEs requiring dose reductions or interruptions	1	5	6	5

## Statistical analyses

No statistical analyses for this end point

## Primary: Maximum concentration (Cmax) of dabrafenib

End point title Maximum concentration (Cmax) of dabrafenib<sup>[3][4]</sup>

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 apply to Part 1 (Dose Escalation)

<b>End point values</b>	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				
geometric mean (geometric coefficient of variation)				
Week 1 Day 1	1820 (± 38.0)	1250 (± 61.5)	1250 (± 529.9)	1900 (± 45.0)
Week 3 Day 15	1470 (± 37.7)	1260 (± 48.1)	1580 (± 49.2)	1710 (± 56.4)

<b>End point values</b>	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	31		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Week 1 Day 1	1340 (± 82.6)	1550 (± 56.8)		
Week 3 Day 15	1450 (± 57.8)	1310 (± 49.4)		

## 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 <sup>[5][6]</sup>
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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.

End point type	Primary
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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: Only apply to Part 1 (Dose Escalation)

[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 apply to Part 1 (Dose Escalation)

<b>End point values</b>	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 <sup>[7]</sup>	0 <sup>[8]</sup>	0 <sup>[9]</sup>	0 <sup>[10]</sup>
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	()	()	()	()

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 <sup>[11]</sup>
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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
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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 apply to Part 1 (Dose Escalation)

<b>End point values</b>	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				
geometric mean (geometric coefficient of variation)				
dabrafenib	11.9 (± 276.5)	39.8 (± 176.1)	50.7 (± 121.0)	11.0 (± 67.5)
hydroxy-dabrafenib	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

carboxy-dabrafenib	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
desmethyl-dabrafenib	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

<b>End point values</b>	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	29		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
dabrafenib	42.7 (± 135.9)	22.8 (± 209.5)		
hydroxy-dabrafenib	999 (± 999)	999 (± 999)		
carboxy-dabrafenib	999 (± 999)	999 (± 999)		
desmethyl-dabrafenib	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 <sup>[12]</sup>
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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.

End point type	Secondary
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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 apply to Part 1 (Dose Escalation)

<b>End point values</b>	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 <sup>[13]</sup>	0 <sup>[14]</sup>	0 <sup>[15]</sup>	0 <sup>[16]</sup>
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	()	()	()	()

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<sup>[17]</sup>

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.

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 apply to Part 1 (Dose Escalation)

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 <sup>[18]</sup>	0 <sup>[19]</sup>	0 <sup>[20]</sup>	0 <sup>[21]</sup>
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

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

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

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

[21] - No reliable AUC(0-tau) 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<sup>[22]</sup>

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.

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 apply to Part 1 (Dose Escalation)

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 <sup>[23]</sup>	0 <sup>[24]</sup>	0 <sup>[25]</sup>	0 <sup>[26]</sup>
Units: mL/hr				
geometric mean (geometric coefficient of variation)	()	()	()	()

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<sup>[27]</sup>

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 apply to Part 1 (Dose Escalation)

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				
geometric mean (geometric coefficient of variation)				
hydroxy-dabrafenib @ Week 1 Day 1	811 (± 24.7)	662 (± 66.7)	473 (± 1643.7)	1370 (± 43.9)
hydroxy-dabrafenib @ Week 3 Day 15	673 (± 62.8)	726 (± 37.6)	752 (± 32.8)	1010 (± 51.5)
carboxy-dabrafenib @ Week 1 Day 1	1720 (± 90.6)	1300 (± 55.7)	824 (± 291.3)	4250 (± 67.0)
carboxy-dabrafenib @ Week 3 Day 15	4700 (± 51.7)	6410 (± 28.0)	9650 (± 35.9)	11200 (± 28.4)

desmethyl-dabrafenib @ Week 1 Day 1	13.0 (± 27.3)	6.55 (± 80.5)	15.4 (± 103.9)	23.7 (± 53.8)
desmethyl-dabrafenib @ Week 3 Day 15	194 (± 219.4)	311 (± 78.9)	317 (± 324.9)	238 (± 45.6)

<b>End point values</b>	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	31		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
hydroxy-dabrafenib @ Week 1 Day 1	694 (± 77.9)	894 (± 58.2)		
hydroxy-dabrafenib @ Week 3 Day 15	772 (± 50.1)	711 (± 43.4)		
carboxy-dabrafenib @ Week 1 Day 1	1650 (± 161.2)	2330 (± 97.6)		
carboxy-dabrafenib @ Week 3 Day 15	8280 (± 45.9)	7970 (± 30.0)		
desmethyl-dabrafenib @ Week 1 Day 1	10.7 (± 159.4)	10.1 (± 88.7)		
desmethyl-dabrafenib @ Week 3 Day 15	328 (± 38.8)	274 (± 77.4)		

## 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 <sup>[28]</sup>
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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
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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 apply to Part 1 (Dose Escalation)

<b>End point values</b>	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 @ Week 1 Day 1	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 @ Week 3 Day 15	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 @ Week 1 Day 1	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 @ Week 3 Day 15	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 @ Week 1 Day 1	4.00 (4.00 to 4.00)			
carboxy-dabrafenib @ Week 3 Day 15	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 @ Week 1 Day 1	4.00 (4.00 to 4.00)			
desmethyl-dabrafenib @ Week 3 Day 15	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)

<b>End point values</b>	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 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 @ Week 1 Day 1	2.00 (0.50 to 4.00)	2.00 (0.50 to 4.00)		
dabrafenib @ Week 3 Day 15	2.00 (1.00 to 6.00)	2.00 (1.00 to 4.00)		
hydroxy-dabrafenib @ Week 1 Day 1	4.00 (2.00 to 4.00)	4.00 (2.00 to 4.00)		
hydroxy-dabrafenib @ Week 3 Day 15	2.00 (1.00 to 6.00)	2.00 (1.00 to 4.00)		
carboxy-dabrafenib @ Week 1 Day 1	4.00 (0.50 to 4.00)	4.00 (4.00 to 4.00)		
carboxy-dabrafenib @ Week 3 Day 15	4.00 (0.00 to 8.00)	4.00 (2.00 to 8.00)		
desmethyl-dabrafenib @ Week 1 Day 1	4.00 (0.50 to 4.00)	4.00 (4.00 to 4.00)		
desmethyl-dabrafenib @ Week 3 Day 15	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 (T<sub>1/2</sub>) of dabrafenib and its metabolites

End point title	Elimination half life (T <sub>1/2</sub> ) of dabrafenib and its metabolites <sup>[29]</sup>
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End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. T<sub>1/2</sub> 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
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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 apply to Part 1 (Dose Escalation)

<b>End point values</b>	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	1.98 (± 0.687)	2.85 (± 1.58)	2.74 (± 0.840)	1.56 (± 0.359)
hydroxy-dabrafenib	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
carboxy-dabrafenib	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
desmethyl-dabrafenib	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

<b>End point values</b>	Part 2 (Tumor Expansion): All patients at RP2D of 5.25 mg/kg	Part 2 (Tumor Expansion): All patients at RP2D of 4,5 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	25		
Units: Hour (hr)				
arithmetic mean (standard deviation)				
dabrafenib	2.54 (± 2.44)	3.03 (± 2.27)		
hydroxy-dabrafenib	999 (± 999)	999 (± 999)		
carboxy-dabrafenib	999 (± 999)	999 (± 999)		
desmethyl-dabrafenib	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) <sup>[30]</sup>
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End point description:

The distribution of adverse events was 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
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End point timeframe:

From study treatment start date till 28 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: Secondary endpoint "Incidence of treatment emergent Adverse Events (AEs) in Part 2 (Tumor Specific Expansion)" only apply to Part 2.

<b>End point values</b>	Part 2 (Tumor specific expansion): Cohort 1 (LGG)	Part 2 (Tumor specific expansion): Cohort 2 (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	0	1	0	0
On-treatment deaths	0	0	0	0
Adverse Events (AEs)	17	26	11	2
AEs suspected to be drug related	16	26	11	0
Serious Adverse Events (SAEs)	7	13	6	0
SAEs suspected to be drug related	1	3	2	0
Fatal SAEs	0	1	0	0
Fatal SAEs suspected to be drug related	0	0	0	0
AEs leading to discontinuation	2	1	1	0
AEs requiring dose interruptions	10	13	7	2
AEs requiring dose reductions	2	4	2	1
AEs requiring dose reductions or interruptions	10	13	7	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 <sup>[31]</sup>
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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
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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 apply to Low Grade Glioma (LLG) subset of subjects

<b>End point values</b>	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 specific expansion): Cohort 1 (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

<b>End point values</b>	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 <sup>[32]</sup>
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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
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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 apply to High Grade Glioma (HGG) subset of subjects

<b>End point values</b>	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 2 (Tumor specific expansion): Cohort 2 (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

<b>End point values</b>	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 weight on total apparent clearance (CL/F) of dabrafenib estimated with a PopPK model

End point title	Effect of weight on total apparent clearance (CL/F) of dabrafenib estimated with a PopPK model
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End point description:

The population pharmacokinetic (PopPK) model of Dabrafenib can be described using a two-compartment model with a delayed 1st order absorption ( $Alag_1$ ,  $K_a$ ) and an inducible elimination (CL/F) that consists of a base clearance (constant over time,  $CL_0/F$ ) and a dose- and time-dependent inducible clearance ( $CL_{ind}/F$ ). The PopPK analysis examined the influence of demographics (i.e., weight) on the pharmacokinetics of dabrafenib. The effect of weight on total apparent clearance (CL/F) of dabrafenib estimated with the PopPK model is summarized in this record.

End point type	Secondary
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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.

<b>End point values</b>	Part 1 and Part 2 – All participants with PK data			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: coefficient				
number (not applicable)	0.223			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect of weight on volume of distribution (V/F) of dabrafenib estimated with a PopPK model

End point title	Effect of weight on volume of distribution (V/F) of dabrafenib estimated with a PopPK model
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End point description:

The population pharmacokinetic (PopPK) model of Dabrafenib can be described using a two-compartment model with a delayed 1st order absorption ( $Alag_1$ ,  $K_a$ ) and an inducible elimination (CL/F) that consists of a base clearance (constant over time,  $CL_0/F$ ) and a dose- and time-dependent inducible clearance ( $CL_{ind}/F$ ). The PopPK analysis examined the influence of demographics (i.e., weight) on the pharmacokinetics of dabrafenib. The effect of weight on volume of distribution (V/F) of dabrafenib

estimated with the PopPK model is summarized in this record.

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.	

<b>End point values</b>	Part 1 and Part 2 – All participants with PK data			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: coefficient				
number (not applicable)	0.593			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect of weight on absorption rate (ka) of dabrafenib estimated with a PopPK model

End point title	Effect of weight on absorption rate (ka) of dabrafenib estimated with a PopPK model
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End point description:

The population pharmacokinetic (PopPK) model of Dabrafenib can be described using a two-compartment model with a delayed 1st order absorption ( $Alag1$ ,  $Ka$ ) and an inducible elimination ( $CL/F$ ) that consists of a base clearance (constant over time,  $CL0/F$ ) and a dose- and time-dependent inducible clearance ( $CLind/F$ ). The PopPK analysis examined the influence of demographics (i.e., weight) on the pharmacokinetics of dabrafenib. The effect of weight on absorption rate (ka) of dabrafenib estimated with a PopPK model is summarized in this record.

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.	

<b>End point values</b>	Part 1 and Part 2 – All participants with PK data			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: coefficient	999			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect of weight on coefficients for significant covariates of dabrafenib estimated with a PopPK model

End point title	Effect of weight on coefficients for significant covariates of dabrafenib estimated with a PopPK model
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End point description:

The population pharmacokinetic (PopPK) model of Dabrafenib can be described using a two-compartment model with a delayed 1st order absorption ( $Alag_1$ ,  $K_a$ ) and an inducible elimination ( $CL/F$ ) that consists of a base clearance (constant over time,  $CL_0/F$ ) and a dose- and time-dependent inducible clearance ( $CL_{ind}/F$ ). The PopPK analysis examined the influence of demographics (i.e., weight) on the pharmacokinetics of dabrafenib. The effect of weight on coefficients for significant covariates of dabrafenib estimated with a PopPK model is summarized in this record.

End point type	Secondary
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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	Part 1 and Part 2 – All participants with PK data			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: coefficient	999			

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: All collected deaths in Parts I and II

End point title	All collected deaths in Parts I and II
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End point description:

On treatment deaths were collected from FPFT up to 28 days after study drug discontinuation, for a maximum duration of 360 weeks in Part I (treatment duration ranged from 5.6 to 356.0 weeks) and a maximum duration of 300 weeks in Part II (treatment duration ranged from 0.3 to 296.0 weeks). Deaths post treatment survival follow up were collected after the on-treatment period, up to approximately 7 years. Patients who didn't die during the on-treatment period and had not stopped study participation at the time of data cut-off (end of study) were censored.

End point type	Post-hoc
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End point timeframe:

up to 360 weeks (on-treatment in Part I), up to 300 weeks (on-treatment in Part II), up to approximately 7 years (study duration)

<b>End point values</b>	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				
On-treatment deaths	0	0	0	1
Post-treatment deaths	0	0	0	0
All deaths	0	0	0	1

<b>End point values</b>	Part 2 (Tumor specific expansion): Cohort 1 (LGG)	Part 2 (Tumor specific expansion): Cohort 2 (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				
On-treatment deaths	0	0	0	0
Post-treatment deaths	0	1	0	0
All deaths	0	1	0	0

### 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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### Reporting groups

Reporting group title	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)
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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 mg/kg)
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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)
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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)
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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 3 (LCH)
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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 2 High-Grade Gliomas (HGG)
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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)
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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 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.	

<b>Serious adverse events</b>	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	0 / 3 (0.00%)	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 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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
<b>Overdose</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Shunt malfunction</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Stroke-like migraine attacks after radiation therapy</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Cardiac disorders</b>			
<b>Tachycardia</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Nervous system disorders</b>			
<b>Ataxia</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Depressed level of consciousness</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Haemorrhage intracranial</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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

Headache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Disseminated intravascular coagulation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Arthralgia</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pain in extremity</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
<b>Appendicitis</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Bacteraemia</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Catheter site infection</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Corynebacterium infection</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Croup infectious</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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 / 10 (0.00%)	0 / 3 (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	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal bacteraemia			

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

subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Hyponatraemia</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (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
<b>Hypophagia</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor expansion): Cohort 3 (LCH)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	3 / 6 (50.00%)	6 / 11 (54.55%)	13 / 28 (46.43%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
<b>Epstein-Barr virus associated lymphoma</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Metastases to meninges</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Tumour haemorrhage</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Vascular disorders</b>			
<b>Hypotension</b>			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>General disorders and administration site conditions</b>			
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>General physical health deterioration</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Pyrexia</b>			
subjects affected / exposed	1 / 6 (16.67%)	5 / 11 (45.45%)	4 / 28 (14.29%)
occurrences causally related to treatment / all	0 / 1	1 / 8	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Respiratory, thoracic and mediastinal disorders</b>			
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Product issues</b>			
Device occlusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Investigations</b>			
Blood culture positive			
subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Injury, poisoning and procedural complications</b>			
Accidental overdose			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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 / 11 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke-like migraine attacks after radiation therapy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac disorders</b>			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Nervous system disorders</b>			
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
Depressed level of consciousness			

subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
<b>Haemorrhage intracranial</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Headache</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	3 / 28 (10.71%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hydrocephalus</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Intracranial pressure increased</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Meningeal disorder</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Paraesthesia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Presyncope</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Seizure</b>			

subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Somnolence</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Blood and lymphatic system disorders</b>			
<b>Disseminated intravascular coagulation</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Febrile neutropenia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Gastrointestinal disorders</b>			
<b>Gastritis</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Vomiting</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Skin and subcutaneous tissue disorders</b>			
<b>Dermatitis bullous</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Pityriasis rosea</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rash maculo-papular subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corynebacterium infection			

subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Croup infectious</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Device related infection</b>			
subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	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
<b>Gastroenteritis</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Herpes zoster</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Infection</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Influenza</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Oral herpes</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Pharyngitis streptococcal</b>			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Pneumonia</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pseudomonal bacteraemia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Respiratory tract infection</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Rhinitis</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Salmonellosis</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Skin infection</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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
<b>Staphylococcal infection</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Upper respiratory tract infection</b>			

subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (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
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (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

<b>Serious adverse events</b>	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)	Part 2 (Tumor expansion): Cohort 4 Miscellaneous tumors	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 17 (41.18%)	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 / 17 (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 / 17 (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	
<b>Tumour haemorrhage</b>			
subjects affected / exposed	0 / 17 (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	
<b>Vascular disorders</b>			
<b>Hypotension</b>			
subjects affected / exposed	0 / 17 (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	
<b>General disorders and administration site conditions</b>			
<b>Disease progression</b>			
subjects affected / exposed	0 / 17 (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	
<b>General physical health deterioration</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pyrexia</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Hypoxia</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Product issues</b>			
<b>Device occlusion</b>			

subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Investigations</b>			
Blood culture positive			
subjects affected / exposed	0 / 17 (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	
Ejection fraction decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Injury, poisoning and procedural complications</b>			
Accidental overdose			
subjects affected / exposed	0 / 17 (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	
Overdose			
subjects affected / exposed	0 / 17 (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 / 17 (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 / 17 (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	
<b>Cardiac disorders</b>			
Tachycardia			

subjects affected / exposed	0 / 17 (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	
<b>Nervous system disorders</b>			
<b>Ataxia</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Depressed level of consciousness</b>			
subjects affected / exposed	0 / 17 (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	
<b>Haemorrhage intracranial</b>			
subjects affected / exposed	0 / 17 (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	
<b>Headache</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hydrocephalus</b>			
subjects affected / exposed	0 / 17 (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	
<b>Intracranial pressure increased</b>			
subjects affected / exposed	0 / 17 (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	
<b>Meningeal disorder</b>			
subjects affected / exposed	0 / 17 (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	
<b>Paraesthesia</b>			

subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 17 (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	0 / 17 (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	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 17 (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 / 17 (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 / 17 (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	0 / 17 (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 and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pityriasis rosea			
subjects affected / exposed	0 / 17 (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	
Rash maculo-papular			
subjects affected / exposed	0 / 17 (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 / 17 (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 / 17 (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 / 17 (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 / 17 (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 / 17 (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	
<b>Catheter site infection</b>			
subjects affected / exposed	0 / 17 (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	
<b>Corynebacterium infection</b>			
subjects affected / exposed	0 / 17 (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	
<b>Croup infectious</b>			
subjects affected / exposed	0 / 17 (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	
<b>Device related infection</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastroenteritis</b>			
subjects affected / exposed	0 / 17 (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	
<b>Herpes zoster</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infection</b>			
subjects affected / exposed	0 / 17 (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	
<b>Influenza</b>			

subjects affected / exposed	0 / 17 (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	
Oral herpes			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 17 (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 / 17 (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	0 / 17 (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	
Salmonellosis			
subjects affected / exposed	0 / 17 (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 / 17 (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	
<b>Staphylococcal infection</b>			
subjects affected / exposed	0 / 17 (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	
<b>Upper respiratory tract infection</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Varicella</b>			
subjects affected / exposed	0 / 17 (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	
<b>Metabolism and nutrition disorders</b>			
<b>Dehydration</b>			
subjects affected / exposed	0 / 17 (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	
<b>Hyponatraemia</b>			
subjects affected / exposed	0 / 17 (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	
<b>Hypophagia</b>			
subjects affected / exposed	0 / 17 (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 %

<b>Non-serious adverse events</b>	Part 1 (Dose Escalation): Dabrafenib treatment (3.75 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (3 mg/kg)	Part 1 (Dose Escalation): Dabrafenib treatment (4.5 mg/kg)
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 10 (100.00%)	3 / 3 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	4	1	6
Skin papilloma			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Acrochordon			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lip neoplasm			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neoplasm skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Xanthogranuloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	1
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	1	1	2
Haematoma			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Hot flush subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Venous thrombosis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Surgical and medical procedures Steroid therapy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Chills subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	1 / 3 (33.33%) 1	2 / 8 (25.00%) 2
Complication associated with device subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	2 / 8 (25.00%) 2
Face oedema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 13	2 / 3 (66.67%) 2	2 / 8 (25.00%) 2
Gait disturbance subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	0 / 3 (0.00%) 0	1 / 8 (12.50%) 1
Influenza like illness subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 3 (0.00%) 0	1 / 8 (12.50%) 2
Pain			

subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
<b>Pyrexia</b>			
subjects affected / exposed	5 / 10 (50.00%)	3 / 3 (100.00%)	7 / 8 (87.50%)
occurrences (all)	25	6	20
<b>Xerosis</b>			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
<b>Catheter site erythema</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Catheter site extravasation</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Chest pain</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
<b>Facial pain</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
<b>Feeling hot</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
<b>Localised oedema</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Malaise</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Non-cardiac chest pain</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Oedema peripheral</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Peripheral swelling</b>			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	1 / 8 (12.50%) 1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	2
Drug hypersensitivity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypersensitivity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Testicular pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 10 (50.00%)	1 / 3 (33.33%)	4 / 8 (50.00%)
occurrences (all)	8	14	6
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Nasal congestion			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	5	6	7
Oropharyngeal pain			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	1 / 8 (12.50%)
occurrences (all)	7	1	1
Rhinitis allergic			

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

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

Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysphemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Emotional disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hallucination			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Middle insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 10 (40.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	11	1	2
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	4	1	3
Blood alkaline phosphatase decreased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood creatinine decreased			

subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	4
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Haemoglobin increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	3
Lymphocyte count decreased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	6	1	2
Neutrophil count decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	1 / 8 (12.50%)
occurrences (all)	0	8	2
Platelet count decreased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	2	5	3
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Weight increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	4
White blood cell count decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	1	5	0
Activated partial thromboplastin time prolonged			

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

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

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

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

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

subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	5	3	8
Headache			
subjects affected / exposed	8 / 10 (80.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	17	10	14
Paraesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Altered state of consciousness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ataxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dysaesthesia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dysarthria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Dysmetria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Facial nerve disorder			

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

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

Neutrophilia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thrombocytosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	1	4	0
Cerumen impaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Deafness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Excessive cerumen production			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
External ear inflammation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blepharospasm			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dark circles under eyes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry eye			

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

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Vernal keratoconjunctivitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
<b>Gastrointestinal disorders</b>			
Abdominal pain subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 5	1 / 3 (33.33%) 2	1 / 8 (12.50%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 5	1 / 3 (33.33%) 1	2 / 8 (25.00%) 5
Constipation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 3 (33.33%) 1	3 / 8 (37.50%) 9
Diarrhoea subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 3 (0.00%) 0	4 / 8 (50.00%) 8
Dyspepsia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 3 (33.33%) 1	0 / 8 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 7	1 / 3 (33.33%) 2	2 / 8 (25.00%) 8
Oral disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0

Oral pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	5 / 10 (50.00%)	2 / 3 (66.67%)	5 / 8 (62.50%)
occurrences (all)	15	5	11
Angular cheilitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chapped lips			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Cheilitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Cheilosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic gastritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Dental caries			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Duodenitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

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

subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Dermatitis acneiform</b>			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	1
<b>Dermatitis exfoliative generalised</b>			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
<b>Dry skin</b>			
subjects affected / exposed	6 / 10 (60.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	7	1	4
<b>Eczema</b>			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
<b>Erythema</b>			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	9	0	2
<b>Erythema nodosum</b>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Hair texture abnormal</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	3
<b>Hyperkeratosis</b>			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	3 / 8 (37.50%)
occurrences (all)	7	0	3
<b>Keratosis pilaris</b>			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	3	1	5
<b>Macule</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2
<b>Pain of skin</b>			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
<b>Palmar-plantar erythrodysesthesia</b>			

syndrome			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Palmoplantar keratoderma			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Panniculitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Papule			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	3	0	3
Rash			
subjects affected / exposed	4 / 10 (40.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	11	1	4
Rash macular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Rash maculo-papular			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	3	5	5
Rash papular			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	4 / 8 (50.00%)
occurrences (all)	1	1	7
Rash pruritic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin discolouration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1

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

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

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

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

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	1 / 8 (12.50%) 1
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Adrenal insufficiency subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Precocious puberty subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 3 (0.00%) 0	1 / 8 (12.50%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 7	1 / 3 (33.33%) 1	2 / 8 (25.00%) 5
Back pain subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	0 / 3 (0.00%) 0	1 / 8 (12.50%) 2
Muscle spasms subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Muscular weakness subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4	0 / 3 (0.00%) 0	0 / 8 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	0 / 3 (0.00%) 0	1 / 8 (12.50%) 1
Neck pain			

subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Pain in extremity			
subjects affected / exposed	4 / 10 (40.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	12	0	7
Flank pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ligament pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Limb mass			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Muscle contracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal deformity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
<b>Infections and infestations</b>			
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Conjunctivitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	4

Folliculitis			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	5	0	2
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Influenza			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	1	2	4
Parainfluenzae virus infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 3 (66.67%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rash pustular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1

Rhinitis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	2
Rhinovirus infection			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	3
Tinea pedis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	5 / 8 (62.50%)
occurrences (all)	4	7	10
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Viral infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2
COVID-19			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Carbuncle			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Coronavirus infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Croup infectious			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

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

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

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

subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	3 / 8 (37.50%)
occurrences (all)	3	0	3
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Hypercalcaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	7	0	1
Hyperglycaemia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	3 / 8 (37.50%)
occurrences (all)	8	1	5
Hyperkalaemia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	5	0	1
Hypermagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	12	0	3
Hyperuricaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	2 / 8 (25.00%)
occurrences (all)	1	1	2
Hypomagnesaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	6	0	0
Hyponatraemia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	3
Hypophosphataemia			
subjects affected / exposed	3 / 10 (30.00%)	2 / 3 (66.67%)	4 / 8 (50.00%)
occurrences (all)	3	2	5
Folate deficiency			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperchloraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vitamin B12 deficiency			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

<b>Non-serious adverse events</b>	Part 1 (Dose Escalation): Dabrafenib treatment (5.25 mg/kg)	Part 2 (Tumor expansion): Cohort 3 (LCH)	Part 2 (Tumor expansion): Cohort 2 High-Grade Gliomas (HGG)
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 6 (100.00%)	11 / 11 (100.00%)	26 / 28 (92.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	2 / 6 (33.33%)	4 / 11 (36.36%)	8 / 28 (28.57%)
occurrences (all)	2	9	11
Skin papilloma			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	2 / 28 (7.14%)
occurrences (all)	1	1	2
Acrochordon			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Lip neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Neoplasm skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Xanthogranuloma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	1	1	1
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)	1 / 11 (9.09%)	4 / 28 (14.29%)
occurrences (all)	2	1	5
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	3 / 11 (27.27%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Haematoma			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	1 / 28 (3.57%) 1
Hot flush subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Venous thrombosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Surgical and medical procedures Steroid therapy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	6 / 28 (21.43%) 6
Chills subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	1 / 28 (3.57%) 1
Complication associated with device subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Face oedema subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 11 (9.09%) 1	0 / 28 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 7	3 / 11 (27.27%) 6	11 / 28 (39.29%) 13
Gait disturbance subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 11 (18.18%) 2	1 / 28 (3.57%) 1
Pain			

subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
<b>Pyrexia</b>			
subjects affected / exposed	5 / 6 (83.33%)	4 / 11 (36.36%)	10 / 28 (35.71%)
occurrences (all)	12	10	103
<b>Xerosis</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Catheter site erythema</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
<b>Catheter site extravasation</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
<b>Chest pain</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
<b>Facial pain</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Feeling hot</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Localised oedema</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
<b>Malaise</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	1	1	1
<b>Non-cardiac chest pain</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
<b>Oedema peripheral</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Peripheral swelling</b>			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Testicular pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 6 (50.00%)	6 / 11 (54.55%)	8 / 28 (28.57%)
occurrences (all)	10	17	11
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	2
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	3 / 11 (27.27%)	1 / 28 (3.57%)
occurrences (all)	3	5	1
Oropharyngeal pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	3	1	1
Rhinitis allergic			

subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	1 / 28 (3.57%)
occurrences (all)	0	2	1
<b>Rhinorrhoea</b>			
subjects affected / exposed	3 / 6 (50.00%)	3 / 11 (27.27%)	4 / 28 (14.29%)
occurrences (all)	6	3	4
<b>Wheezing</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Adenoidal hypertrophy</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Catarrh</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Dyspnoea</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Hypocapnia</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Laryngeal inflammation</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Productive cough</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Respiratory acidosis</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Respiratory tract congestion</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Restrictive pulmonary disease</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Sleep apnoea syndrome</b>			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	3 / 11 (27.27%)	1 / 28 (3.57%)
occurrences (all)	4	3	1
Depression			
subjects affected / exposed	1 / 6 (16.67%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	3	2	0
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Mood altered			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Affect lability			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Aggression			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Anger			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Dysphemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Emotional disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Middle insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Suicidal ideation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	3 / 11 (27.27%)	0 / 28 (0.00%)
occurrences (all)	4	5	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 11 (27.27%)	2 / 28 (7.14%)
occurrences (all)	4	4	2
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	2	1	1
Blood creatinine decreased			

subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	2 / 6 (33.33%)	5 / 11 (45.45%)	5 / 28 (17.86%)
occurrences (all)	3	13	9
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	2 / 28 (7.14%)
occurrences (all)	1	1	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Haemoglobin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 11 (9.09%)	2 / 28 (7.14%)
occurrences (all)	2	1	2
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	1	8	0
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Weight increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
White blood cell count decreased			
subjects affected / exposed	1 / 6 (16.67%)	4 / 11 (36.36%)	2 / 28 (7.14%)
occurrences (all)	1	13	2
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Blood calcium decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Blood chloride increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
Blood fibrinogen decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Blood luteinising hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood prolactin abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood urea decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0

Carbon dioxide decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 11 (18.18%) 2	0 / 28 (0.00%) 0
Cardiac murmur subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 11 (9.09%) 1	0 / 28 (0.00%) 0
Creatinine urine decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Ejection fraction decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 11 (9.09%) 1	1 / 28 (3.57%) 1
Eosinophil count increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Low density lipoprotein increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Platelet count increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Protein total increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Protein urine present subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Red blood cell count increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	1 / 28 (3.57%) 1
Respiratory rate decreased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Urine analysis abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 6 (16.67%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	2	3	0
Contusion			
subjects affected / exposed	1 / 6 (16.67%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	4	2	0
Fall			
subjects affected / exposed	2 / 6 (33.33%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	2	4	0
Gastrostomy tube site complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Animal bite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Animal scratch			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Clavicle fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Hand fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nail avulsion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Overdose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Scar			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Skin laceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sunburn			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 11 (9.09%) 1	0 / 28 (0.00%) 0
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Wound subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Cardiac disorders			
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	2 / 11 (18.18%) 6	0 / 28 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	1 / 11 (9.09%) 1	1 / 28 (3.57%) 2
Bradycardia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	1 / 28 (3.57%) 1
Cardiac disorder subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Mitral valve incompetence subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 11 (9.09%) 2	0 / 28 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 11 (9.09%) 2	1 / 28 (3.57%) 1
Tricuspid valve disease subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 11 (9.09%) 3	0 / 28 (0.00%) 0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Headache			
subjects affected / exposed	2 / 6 (33.33%)	4 / 11 (36.36%)	10 / 28 (35.71%)
occurrences (all)	11	6	14
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	4 / 28 (14.29%)
occurrences (all)	0	0	6
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	2 / 28 (7.14%)
occurrences (all)	0	2	2
Altered state of consciousness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Dysaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Dysmetria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Facial nerve disorder			

subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Hemianopia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Hypersomnia</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Hypoaesthesia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	2
<b>Lethargy</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
<b>Migraine</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Muscle spasticity</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Nervous system disorder</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Neuropathy peripheral</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Nystagmus</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Oculofacial paralysis</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Partial seizures</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Periodic limb movement disorder</b>			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Vlith nerve paralysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Blood and lymphatic system disorders</b>			
<b>Anaemia</b>			
subjects affected / exposed	3 / 6 (50.00%)	3 / 11 (27.27%)	4 / 28 (14.29%)
occurrences (all)	4	4	5
<b>Leukocytosis</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	2	2	1
<b>Leukopenia</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	0	2	2
<b>Lymphopenia</b>			
subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
<b>Neutropenia</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	3 / 28 (10.71%)
occurrences (all)	1	3	8
<b>Thrombocytopenia</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	1	2	1
<b>Monocytosis</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	4	0

Neutrophilia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Cerumen impaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Deafness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Excessive cerumen production			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
External ear inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Eye pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Blepharospasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dark circles under eyes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dry eye			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
<b>Eye pruritus</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Hypermetropia</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
<b>Keratitis</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Myopia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Ocular hyperaemia</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
<b>Optic nerve disorder</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Papilloedema</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Periorbital swelling</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
<b>Photophobia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Retinal exudates</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
<b>Scleral disorder</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Uveitis</b>			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vernal keratoconjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
<b>Gastrointestinal disorders</b>			
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 11 (9.09%)	3 / 28 (10.71%)
occurrences (all)	13	3	5
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	4 / 11 (36.36%)	2 / 28 (7.14%)
occurrences (all)	1	6	2
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)	4 / 11 (36.36%)	4 / 28 (14.29%)
occurrences (all)	8	10	4
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	2
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	4 / 11 (36.36%)	7 / 28 (25.00%)
occurrences (all)	9	8	8
Oral disorder			
subjects affected / exposed	2 / 6 (33.33%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0

Oral pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	4 / 6 (66.67%)	9 / 11 (81.82%)	10 / 28 (35.71%)
occurrences (all)	20	20	17
Angular cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Chapped lips			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cheilosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Chronic gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Duodenal ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Duodenitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Glossodynia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	3
Oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Oral mucosal eruption			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Tongue ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 11 (27.27%)	3 / 28 (10.71%)
occurrences (all)	0	3	3
Blister			

subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
<b>Dermatitis acneiform</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Dermatitis exfoliative generalised</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Dry skin</b>			
subjects affected / exposed	4 / 6 (66.67%)	5 / 11 (45.45%)	9 / 28 (32.14%)
occurrences (all)	8	8	9
<b>Eczema</b>			
subjects affected / exposed	2 / 6 (33.33%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	2	1	1
<b>Erythema</b>			
subjects affected / exposed	1 / 6 (16.67%)	3 / 11 (27.27%)	2 / 28 (7.14%)
occurrences (all)	1	3	4
<b>Erythema nodosum</b>			
subjects affected / exposed	0 / 6 (0.00%)	3 / 11 (27.27%)	1 / 28 (3.57%)
occurrences (all)	0	3	1
<b>Hair texture abnormal</b>			
subjects affected / exposed	1 / 6 (16.67%)	3 / 11 (27.27%)	1 / 28 (3.57%)
occurrences (all)	1	3	1
<b>Hyperkeratosis</b>			
subjects affected / exposed	2 / 6 (33.33%)	3 / 11 (27.27%)	4 / 28 (14.29%)
occurrences (all)	2	5	4
<b>Keratosis pilaris</b>			
subjects affected / exposed	2 / 6 (33.33%)	0 / 11 (0.00%)	4 / 28 (14.29%)
occurrences (all)	2	0	4
<b>Macule</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
<b>Pain of skin</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
<b>Palmar-plantar erythrodysesthesia</b>			

syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	0	4	1
Palmoplantar keratoderma			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	1	3	1
Panniculitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Papule			
subjects affected / exposed	2 / 6 (33.33%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Pruritus			
subjects affected / exposed	2 / 6 (33.33%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	2	2	1
Rash			
subjects affected / exposed	3 / 6 (50.00%)	3 / 11 (27.27%)	8 / 28 (28.57%)
occurrences (all)	4	4	11
Rash macular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	3 / 28 (10.71%)
occurrences (all)	1	1	3
Rash papular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Skin discolouration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0

Skin disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	1	1	2
Skin hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	3 / 6 (50.00%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	4	1	1
Skin mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Yellow skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Cafe au lait spots			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dermatitis bullous			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0

<p> Dermatitis contact  subjects affected / exposed  occurrences (all) </p>	<p> 1 / 6 (16.67%)  1 </p>	<p> 2 / 11 (18.18%)  3 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Dermatitis diaper  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 1 / 11 (9.09%)  1 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Ecchymosis  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 1 / 28 (3.57%)  1 </p>
<p> Eczema asteatotic  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Ephelides  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Hair colour changes  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 1 / 11 (9.09%)  1 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Hidradenitis  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Hyperhidrosis  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 1 / 11 (9.09%)  1 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Ingrown hair  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Intertrigo  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Keloid scar  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 0 / 28 (0.00%)  0 </p>
<p> Lentigo  subjects affected / exposed  occurrences (all) </p>	<p> 0 / 6 (0.00%)  0 </p>	<p> 0 / 11 (0.00%)  0 </p>	<p> 0 / 28 (0.00%)  0 </p>

Miliaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nail discolouration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Nail pigmentation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Neurodermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Onychomadesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Rash vesicular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Seborrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0

Skin fissures			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin induration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin odour abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Xeroderma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Proteinuria			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	4 / 28 (14.29%)
occurrences (all)	4	2	10
Haemoglobinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Microalbuminuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Renal tubular disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 11 (9.09%) 1	0 / 28 (0.00%) 0
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 11 (9.09%) 1	2 / 28 (7.14%) 2
Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Precocious puberty subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	1 / 11 (9.09%) 1	4 / 28 (14.29%) 7
Back pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	3 / 28 (10.71%) 3
Muscle spasms subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	1 / 28 (3.57%) 1
Muscular weakness subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 11 (0.00%) 0	0 / 28 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 11 (9.09%) 1	0 / 28 (0.00%) 0
Neck pain			

subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 6 (33.33%)	3 / 11 (27.27%)	4 / 28 (14.29%)
occurrences (all)	2	5	5
Flank pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Ligament pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Limb mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Muscle contracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal deformity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
<b>Infections and infestations</b>			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	4 / 11 (36.36%)	2 / 28 (7.14%)
occurrences (all)	1	5	2
Ear infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1

Folliculitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	1	1	1
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	2
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	3 / 28 (10.71%)
occurrences (all)	1	1	5
Otitis media			
subjects affected / exposed	2 / 6 (33.33%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Parainfluenzae virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	4	0	4
Pharyngitis streptococcal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Rash pustular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Rhinitis			
subjects affected / exposed	2 / 6 (33.33%)	3 / 11 (27.27%)	4 / 28 (14.29%)
occurrences (all)	2	12	7
Rhinovirus infection			
subjects affected / exposed	2 / 6 (33.33%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	3	0	0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	3 / 28 (10.71%)
occurrences (all)	0	1	5
Tinea pedis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	4 / 11 (36.36%)	4 / 28 (14.29%)
occurrences (all)	2	4	6
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Carbuncle			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Coronavirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Croup infectious			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	2	1	0

Enterobiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Enterovirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Eye infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Furuncle			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Gastritis viral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Groin abscess			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Metapneumovirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	2
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Otitis media acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Pertussis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pitted keratolysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Skin bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Streptococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tinea cruris			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tinea infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tracheostomy infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Viral rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Vulval abscess			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	4 / 6 (66.67%)	2 / 11 (18.18%)	6 / 28 (21.43%)
occurrences (all)	6	2	6
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 11 (27.27%)	3 / 28 (10.71%)
occurrences (all)	1	6	3
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Hypermagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 11 (18.18%)	1 / 28 (3.57%)
occurrences (all)	0	3	1
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Hyperuricaemia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	5	3	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 11 (18.18%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 11 (18.18%)	1 / 28 (3.57%)
occurrences (all)	5	2	1
Hypomagnesaemia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	4	0	1
Hyponatraemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Hypophosphataemia</b>			
subjects affected / exposed	3 / 6 (50.00%)	5 / 11 (45.45%)	4 / 28 (14.29%)
occurrences (all)	5	9	4
<b>Folate deficiency</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Hyperchloraemia</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
<b>Hyperlipidaemia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Hyperphosphataemia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Hypocalcaemia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Iron deficiency</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
<b>Metabolic acidosis</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
<b>Polydipsia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Vitamin B12 deficiency</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 11 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
<b>Vitamin D deficiency</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 11 (9.09%)	1 / 28 (3.57%)
occurrences (all)	0	1	1

<b>Non-serious adverse events</b>	Part 2 (Tumor expansion): Cohort 1 Low-Grade Gliomas (LGG)	Part 2 (Tumor expansion): Cohort 4 Miscellaneous tumors	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	2 / 2 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)	
occurrences (all)	7	0	
Skin papilloma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Acrochordon			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Lip neoplasm			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Neoplasm skin			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Xanthogranuloma			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Hypertension			
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Hypotension			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	5	0	
Haematoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Hot flush subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 2 (0.00%) 0	
Venous thrombosis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Surgical and medical procedures Steroid therapy subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Chills subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Complication associated with device subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Face oedema subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	6 / 17 (35.29%) 7	0 / 2 (0.00%) 0	
Gait disturbance subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Influenza like illness subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Pyrexia			

subjects affected / exposed	11 / 17 (64.71%)	2 / 2 (100.00%)
occurrences (all)	23	2
Xerosis		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Catheter site erythema		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Catheter site extravasation		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Chest pain		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Facial pain		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Feeling hot		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Localised oedema		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Malaise		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Non-cardiac chest pain		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Oedema peripheral		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Peripheral swelling		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Immune system disorders		

Seasonal allergy subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Hypersensitivity subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 2 (0.00%) 0	
Reproductive system and breast disorders			
Amenorrhoea subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Testicular pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 4	0 / 2 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3	0 / 2 (0.00%) 0	
Nasal congestion subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3	0 / 2 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Rhinorrhoea			

subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)
occurrences (all)	3	0
Wheezing		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Adenoidal hypertrophy		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Catarrh		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Dyspnoea		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Hypocapnia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Laryngeal inflammation		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
Productive cough		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Respiratory acidosis		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Respiratory tract congestion		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Restrictive pulmonary disease		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Sleep apnoea syndrome		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Sneezing		

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Tachypnoea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Anxiety subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Depression subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Mood altered subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Affect lability subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Aggression subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Anger subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Attention deficit hyperactivity disorder			

subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Dysphemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Emotional disorder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Hallucination			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Irritability			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Middle insomnia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Suicidal ideation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Blood creatinine decreased			

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

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

Carbon dioxide decreased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0
Cardiac murmur subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0
Creatinine urine decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0
Ejection fraction decreased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0
Eosinophil count increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0
Low density lipoprotein increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0
Platelet count increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0
Protein total increased subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3	0 / 2 (0.00%) 0
Protein urine present subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3	0 / 2 (0.00%) 0
Red blood cell count increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0
Respiratory rate decreased		

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Transaminases increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 2 (50.00%) 1	
Urine albumin/creatinine ratio increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Urine analysis abnormal subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	0 / 2 (0.00%) 0	
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Fall subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Gastrostomy tube site complication subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Procedural pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Animal bite subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Animal scratch			

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

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

subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Dizziness</b>		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	3	0
<b>Headache</b>		
subjects affected / exposed	8 / 17 (47.06%)	0 / 2 (0.00%)
occurrences (all)	18	0
<b>Paraesthesia</b>		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
<b>Seizure</b>		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Somnolence</b>		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Syncope</b>		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Altered state of consciousness</b>		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Ataxia</b>		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
<b>Dysaesthesia</b>		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Dysarthria</b>		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Dysmetria</b>		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
<b>Facial nerve disorder</b>		

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

subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vlith nerve paralysis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Visual field defect			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 17 (29.41%)	0 / 2 (0.00%)	
occurrences (all)	9	0	
Leukocytosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Leukopenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Lymphopenia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Thrombocytopenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Monocytosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

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

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

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Vernal keratoconjunctivitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
<b>Gastrointestinal disorders</b>			
Abdominal pain subjects affected / exposed occurrences (all)	4 / 17 (23.53%) 7	0 / 2 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	6 / 17 (35.29%) 12	0 / 2 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3	0 / 2 (0.00%) 0	
Oral disorder subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	0 / 2 (0.00%) 0	

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

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

subjects affected / exposed	4 / 17 (23.53%)	0 / 2 (0.00%)
occurrences (all)	5	0
Dermatitis acneiform		
subjects affected / exposed	4 / 17 (23.53%)	0 / 2 (0.00%)
occurrences (all)	4	0
Dermatitis exfoliative generalised		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Dry skin		
subjects affected / exposed	7 / 17 (41.18%)	0 / 2 (0.00%)
occurrences (all)	10	0
Eczema		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	5	0
Erythema		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Erythema nodosum		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	2	0
Hair texture abnormal		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
Hyperkeratosis		
subjects affected / exposed	4 / 17 (23.53%)	0 / 2 (0.00%)
occurrences (all)	7	0
Keratosis pilaris		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Macule		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Pain of skin		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	3	0
Palmar-plantar erythrodysesthesia		

syndrome		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Palmoplantar keratoderma		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Panniculitis		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	5	0
Papule		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Pruritus		
subjects affected / exposed	5 / 17 (29.41%)	0 / 2 (0.00%)
occurrences (all)	6	0
Rash		
subjects affected / exposed	6 / 17 (35.29%)	0 / 2 (0.00%)
occurrences (all)	11	0
Rash macular		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Rash maculo-papular		
subjects affected / exposed	5 / 17 (29.41%)	0 / 2 (0.00%)
occurrences (all)	10	0
Rash papular		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
Rash pruritic		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Seborrhoeic dermatitis		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Skin discolouration		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0

Skin disorder		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
Skin exfoliation		
subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)
occurrences (all)	3	0
Skin hyperpigmentation		
subjects affected / exposed	4 / 17 (23.53%)	0 / 2 (0.00%)
occurrences (all)	5	0
Skin hypertrophy		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Skin lesion		
subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)
occurrences (all)	3	0
Skin mass		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Urticaria		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Yellow skin		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Cafe au lait spots		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Dermal cyst		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Dermatitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Dermatitis bullous		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0

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

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

Skin fissures			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Skin induration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Skin odour abnormal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Xeroderma			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)	
occurrences (all)	7	0	
Haemoglobinuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Microalbuminuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Polyuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Renal tubular disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Urinary incontinence			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Urinary tract pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 6	0 / 2 (0.00%) 0	
Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Precocious puberty subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 2 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 17 (23.53%) 8	0 / 2 (0.00%) 0	
Back pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Muscle spasms subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 6	0 / 2 (0.00%) 0	
Muscular weakness subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	0 / 2 (0.00%) 0	
Neck pain			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 6	0 / 2 (0.00%) 0	
Flank pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Ligament pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Limb mass subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Muscle contracture subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Musculoskeletal deformity subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
<b>Infections and infestations</b>			
Bronchitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 2 (0.00%) 0	
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 2 (0.00%) 0	
Ear infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 2 (50.00%) 1	

Folliculitis		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Gastroenteritis		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Herpes zoster		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Influenza		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	3	0
Nasopharyngitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	2	0
Otitis media		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Parainfluenzae virus infection		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Pharyngitis streptococcal		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Pneumonia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Rash pustular		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Respiratory syncytial virus infection		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0

Rhinitis		
subjects affected / exposed	2 / 17 (11.76%)	1 / 2 (50.00%)
occurrences (all)	2	1
Rhinovirus infection		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Skin infection		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	8	0
Tinea pedis		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Upper respiratory tract infection		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Urinary tract infection		
subjects affected / exposed	4 / 17 (23.53%)	0 / 2 (0.00%)
occurrences (all)	4	0
Viral infection		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
COVID-19		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Candida infection		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Carbuncle		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Coronavirus infection		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Croup infectious		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0

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

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

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

subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Dehydration		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Hypercalcaemia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	4	0
Hyperglycaemia		
subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)
occurrences (all)	6	0
Hyperkalaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Hypermagnesaemia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
Hypernatraemia		
subjects affected / exposed	3 / 17 (17.65%)	0 / 2 (0.00%)
occurrences (all)	6	0
Hyperuricaemia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	2	0
Hypoalbuminaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Hypoglycaemia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	3	0
Hypokalaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Hypomagnesaemia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 2 (0.00%)
occurrences (all)	8	0
Hyponatraemia		

subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Hypophosphataemia		
subjects affected / exposed	3 / 17 (17.65%)	1 / 2 (50.00%)
occurrences (all)	3	1
Folate deficiency		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Hyperchloraemia		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Hyperlipidaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Hyperphosphataemia		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Hypocalcaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Iron deficiency		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Metabolic acidosis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Polydipsia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 2 (0.00%)
occurrences (all)	1	0
Vitamin B12 deficiency		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0
Vitamin D deficiency		
subjects affected / exposed	0 / 17 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	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 $\leq 1$ 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 $\geq 12$ 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 $\geq 12$ 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.novfor> for complete trial results.

Notes: