



Clinical trial results:

A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma

Summary

EudraCT number	2015-002468-18
Trial protocol	GB DK DE NL IT
Global end of trial date	19 June 2021

Results information

Result version number	v2 (current)
This version publication date	13 July 2024
First version publication date	11 January 2022
Version creation reason	• Correction of full data set Correction of full data set

Trial information

Trial identification

Sponsor protocol code	EZH-102
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02601937
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Epizyme, Inc.
Sponsor organisation address	400 Technology Square, 4th Floor, Cambridge, United States, 02139
Public contact	Shefali Agarwal, MBBS, MPH, MIS, Epizyme, Inc., 001 855500-1011, clinicaltrials@epizyme.com
Scientific contact	Shefali Agarwal, MBBS, MPH, MIS, Epizyme, Inc., 001 855500-1011, clinicaltrials@epizyme.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-003055-PIP01-21
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 October 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Dose Escalation: To determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) of tazemetostat when administered as an oral suspension twice daily (BID) in pediatric subjects with relapsed/refractory rhabdoid tumors, integrase interactor 1 (INI1)-negative tumors or synovial sarcoma.

Dose Expansion: To evaluate the antitumor activity of tazemetostat as assessed by overall response rate (ORR) in pediatric subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria.

Protection of trial subjects:

The procedures set out in the study protocol pertaining to the conduct, evaluation, and documentation of this study were designed to ensure that the Sponsor and Investigators are by Good Clinical Practice (GCP) as described in the International Conference on Harmonisation (ICH) Tripartite Guideline E6. Compliance with these regulations also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study was also carried out in keeping with local legal and regulatory requirements. Subject confidentiality was strictly held in trust by the Sponsor and/or their designee(s), participating Investigators, and site staff.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	United States: 55
Country: Number of subjects enrolled	Canada: 3

Worldwide total number of subjects	109
EEA total number of subjects	37

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	17
Children (2-11 years)	62
Adolescents (12-17 years)	27
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

07 January 2016 – 19 June 2021; Medical clinics, hospitals, and academic research centers.

Pre-assignment

Screening details:

A signed, written informed consent (and assent, if applicable) must be obtained prior to any study-specific assessments or procedures being performed. All Screening assessments must be performed within 14 days prior to enrollment (Screening Period extends from Day -14 to Day -1).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose Escalation Level 1

Arm description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 240 milligrams per square meter (mg/m²) BID in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Escalation Level 2
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Arm description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 300 mg/m² BID in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Escalation Level 3
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Arm description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 400 mg/m² BID in continuous 28-day cycles.

Arm type	Experimental
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Investigational medicinal product name	Tazemostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Escalation Level 4
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Arm description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 520 mg/m² BID in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Escalation Level 5
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Arm description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 700 mg/m² BID in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Escalation Level 6
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Arm description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 900 mg/m² BID in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Escalation Level 7
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Arm description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with

SS18-SSX rearrangement received oral tazemetostat 1200 mg/m² BID in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Expansion Cohort 1
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Arm description:

Subjects with atypical teratoid rhabdoid tumor (ATRT) who participated in the dose expansion portion of the study received 1200 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Expansion Cohort 2
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Arm description:

Subjects with malignant rhabdoid tumor (MRT)/ rhabdoid tumor of kidney (RTK)/select tumors with rhabdoid features who participated in the dose expansion portion of the study. Subjects whose disease was without central nervous system (CNS) involvement received 520 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Expansion Cohort 3
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Arm description:

Subjects with INI-negative tumors who participated in the dose expansion portion of the study. Subjects whose disease was without central nervous system (CNS) involvement received 520 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received tazemetostat oral suspension. The amount of tazemetostat oral suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Subjects received oral suspension at the assigned dose twice daily.

Arm title	Dose Expansion Cohort 4
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Arm description:

Subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement received 800 mg/m² tazemetostat three times daily (TID) orally in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemostat
Investigational medicinal product code	EPZ-6438
Other name	E7438
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects in Dose Expansion Cohort 4 received tazemetostat tablet formulation, 800 mg/m² three times daily (2400 mg/m²/day equivalent to 1200 mg/m² BID).

Number of subjects in period 1	Dose Escalation Level 1	Dose Escalation Level 2	Dose Escalation Level 3
Started	8	6	6
Completed	0	0	0
Not completed	8	6	6
Physician decision	-	-	-
death	-	-	-
unknown	-	-	-
Adverse event, non-fatal	-	-	-
Subject refused further treatment of study drug	1	-	-
Unacceptable toxicity	-	-	1
Disease Progression	7	6	5

Number of subjects in period 1	Dose Escalation Level 4	Dose Escalation Level 5	Dose Escalation Level 6
Started	7	6	6
Completed	1	0	1
Not completed	6	6	5
Physician decision	-	-	-
death	-	-	-
unknown	-	-	-
Adverse event, non-fatal	-	-	1
Subject refused further treatment of study drug	-	-	-
Unacceptable toxicity	-	-	-

Disease Progression	6	6	4
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Number of subjects in period 1	Dose Escalation Level 7	Dose Expansion Cohort 1	Dose Expansion Cohort 2
Started	7	19	20
Completed	0	1	0
Not completed	7	18	20
Physician decision	-	-	-
death	-	-	1
unknown	-	-	2
Adverse event, non-fatal	-	-	-
Subject refused further treatment of study drug	1	2	-
Unacceptable toxicity	-	-	-
Disease Progression	6	16	17

Number of subjects in period 1	Dose Expansion Cohort 3	Dose Expansion Cohort 4
Started	18	6
Completed	0	1
Not completed	18	5
Physician decision	1	1
death	-	-
unknown	2	-
Adverse event, non-fatal	1	-
Subject refused further treatment of study drug	-	-
Unacceptable toxicity	-	-
Disease Progression	14	4

Baseline characteristics

Reporting groups

Reporting group title	Dose Escalation Level 1
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 240 milligrams per square meter (mg/m ²) BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 2
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 300 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 3
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 400 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 4
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 520 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 5
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 700 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 6
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 900 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 7
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 1200 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 1
Reporting group description: Subjects with atypical teratoid rhabdoid tumor (ATRT) who participated in the dose expansion portion of the study received 1200 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 2
Reporting group description: Subjects with malignant rhabdoid tumor (MRT)/ rhabdoid tumor of kidney (RTK)/select tumors with rhabdoid features who participated in the dose expansion portion of the study. Subjects whose disease was without central nervous system (CNS) involvement received 520 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 3
Reporting group description: Subjects with INI1-negative tumors who participated in the dose expansion portion of the study. Subjects whose disease was without central nervous system (CNS) involvement received 520 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 4
Reporting group description: Subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement received 800 mg/m ² tazemetostat three times daily (TID) orally in continuous 28-day cycles.	

Reporting group values	Dose Escalation Level 1	Dose Escalation Level 2	Dose Escalation Level 3
Number of subjects	8	6	6
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	4	1	1
Children (2-11 years)	4	0	4
Adolescents (12-17 years)	0	5	1
Adults (18-64 years)	0	0	0
Gender categorical Units: Subjects			
Female	4	4	5
Male	4	2	1
Race Units: Subjects			
Asian	0	0	1
Black or African American	1	0	0
White	7	6	4
Unknown or Not Reported	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	3
Not Hispanic or Latino	8	4	2
Unknown or Not Reported	0	2	1

Reporting group values	Dose Escalation Level 4	Dose Escalation Level 5	Dose Escalation Level 6
Number of subjects	7	6	6
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1	0	1
Children (2-11 years)	6	4	5
Adolescents (12-17 years)	0	2	0
Adults (18-64 years)	0	0	0
Gender categorical Units: Subjects			
Female	5	2	4
Male	2	4	2
Race Units: Subjects			
Asian	1	0	1
Black or African American	1	1	1
White	5	4	4
Unknown or Not Reported	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	7	4	5
Unknown or Not Reported	0	1	1

Reporting group values	Dose Escalation	Dose Expansion	Dose Expansion
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	Level 7	Cohort 1	Cohort 2
Number of subjects	7	19	20
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	2	2	5
Children (2-11 years)	4	15	13
Adolescents (12-17 years)	1	2	2
Adults (18-64 years)	0	0	0
Gender categorical			
Units: Subjects			
Female	2	12	7
Male	5	7	13
Race			
Units: Subjects			
Asian	0	0	1
Black or African American	1	2	0
White	5	14	12
Unknown or Not Reported	1	3	7
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	5	2
Not Hispanic or Latino	5	13	14
Unknown or Not Reported	1	1	4

Reporting group values	Dose Expansion Cohort 3	Dose Expansion Cohort 4	Total
Number of subjects	18	6	109
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	17
Children (2-11 years)	5	2	62
Adolescents (12-17 years)	12	2	27
Adults (18-64 years)	1	2	3
Gender categorical			
Units: Subjects			
Female	11	3	59
Male	7	3	50
Race			
Units: Subjects			
Asian	0	0	4
Black or African American	1	0	8
White	14	4	79
Unknown or Not Reported	3	2	18
Ethnicity			
Units: Subjects			
Hispanic or Latino	4	1	17
Not Hispanic or Latino	12	5	79
Unknown or Not Reported	2	0	13

End points

End points reporting groups

Reporting group title	Dose Escalation Level 1
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 240 milligrams per square meter (mg/m ²) BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 2
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 300 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 3
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 400 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 4
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 520 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 5
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 700 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 6
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 900 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Escalation Level 7
Reporting group description: Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 1200 mg/m ² BID in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 1
Reporting group description: Subjects with atypical teratoid rhabdoid tumor (ATRT) who participated in the dose expansion portion of the study received 1200 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 2
Reporting group description: Subjects with malignant rhabdoid tumor (MRT)/ rhabdoid tumor of kidney (RTK)/select tumors with rhabdoid features who participated in the dose expansion portion of the study. Subjects whose disease was without central nervous system (CNS) involvement received 520 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 3
Reporting group description: Subjects with INI1-negative tumors who participated in the dose expansion portion of the study. Subjects whose disease was without central nervous system (CNS) involvement received 520 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m ² open-label, tazemetostat BID orally in continuous 28-day cycles.	
Reporting group title	Dose Expansion Cohort 4
Reporting group description: Subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement received 800 mg/m ² tazemetostat three times daily (TID) orally in continuous 28-day cycles.	

Subject analysis set title	Overall Dose Escalation
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat at dose Level 1: 240 mg/m² BID, dose level 2: 300 mg/m² BID, dose level 3: 400 mg/m² BID, dose level 4: 520 mg/m² BID, dose level 5: 700 mg/m² BID, dose level 6: 900 mg/m² BID and dose level 7: 1200 mg/m² BID in continuous 28-day cycles.

Primary: Number of Dose-limiting Toxicities (Dose Escalation Only)

End point title	Number of Dose-limiting Toxicities (Dose Escalation Only) ^{[1][2]}
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End point description:

The RP2D in pediatric subjects treated with tazemetostat as determined by the incidence and severity of treatment-emergent adverse events qualifying as protocol-defined dose-limiting toxicities that occurred during the first month of treatment. Dose-Limiting Toxicity (DLT) population included all subjects in the safety population set who experienced a DLT during Cycle 1 or were not removed from Cycle 1 for reasons other than toxicity and did not have an interruption in study treatment for more than 14 days during Cycle 1. Only those subjects with data collected at Cycle 1 are reported.

End point type	Primary
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End point timeframe:

Cycle 1, from the start of study treatment (Day 1) until the end of the first Cycle (Day 28) of treatment

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: Summary statistics were provided for this study. This was a signal findings study that was not powered to make statistical comparisons.

[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: There are 8 different phases in the trial (7 dose escalation phases and the dose expansion phase with 4 cohorts) within the same period (overall study). All 8 phases are encompassed within the baseline period but the dose escalation and dose expansion phases have different end points.

End point values	Dose Escalation Level 1	Dose Escalation Level 2	Dose Escalation Level 3	Dose Escalation Level 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	6
Units: number	0	1	0	0

End point values	Dose Escalation Level 5	Dose Escalation Level 6	Dose Escalation Level 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: number	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR) (dose expansion only)

End point title	Overall Response Rate (ORR) (dose expansion only) ^{[3][4]}
End point description: ORR is defined as the percentage of subjects who achieved a confirmed CR and/or PR defined by RECIST or RANO criteria from the start of tazemetostat treatment until disease progression or the start of subsequent anticancer therapy, whichever occurs first. CR is defined as disappearance of all target and non-target lesions (with all lymph nodes must be non-pathological in size or under 10 millimeters [mm] in short axis) and PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ORR= CR+PR. The ITT population included all subjects who received at least one dose of tazemetostat.	
End point type	Primary
End point timeframe: RECIST assessments performed at screening (within 14 days before start of study intervention) and every 8 weeks post start of dosing, approximately up to 302 weeks	

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: Summary statistics were provided for this study. This was a signal findings study that was not powered to make statistical comparisons.

[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: There are 8 different phases in the trial (7 dose escalation phases and the dose expansion phase with 4 cohorts) within the same period (overall study). All 8 phases are encompassed within the baseline period but the dose escalation and dose expansion phases have different end points.

End point values	Dose Expansion Cohort 1	Dose Expansion Cohort 2	Dose Expansion Cohort 3	Dose Expansion Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	20	18	6
Units: Percentage of participants				
number (not applicable)	26.3	0	16.7	16.7

Statistical analyses

No statistical analyses for this end point

Primary: Recommended phase 2 dose (RP2D) (dose escalation only)

End point title	Recommended phase 2 dose (RP2D) (dose escalation only) ^[5]
End point description: The incidence and severity of treatment-emergent adverse events qualifying as protocol-defined dose-limiting toxicities that occurred during the first month of treatment was used to determine the RP2D and/or MTD in pediatric subjects treated with tazemetostat. The ITT population included all subjects who received at least one dose of tazemetostat.	
End point type	Primary
End point timeframe: Cycle 1, from the start of study treatment (Day 1) until the end of the first Cycle (Day 28) of treatment	

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: Summary statistics were provided for this study. This was a signal findings study that was not powered to make statistical comparisons.

End point values	Overall Dose Escalation			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: mg/m ² BID				
number (not applicable)				
RP2D for subjects with ATRT or CNS involvement	1200			
RP2D for subjects without CNS involvement	520			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR (dose escalation only)

End point title	ORR (dose escalation only) ^[6]
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End point description:

ORR is defined as the percentage of subjects who achieved a confirmed complete response (CR) and/or partial response (PR) defined by response evaluation criteria in solid tumors (RECIST) or response assessment in neuro-oncology (RANO) criteria from the start of tazemetostat treatment until disease progression or the start of subsequent anticancer therapy, whichever occurs first. CR is defined as disappearance of all target and non-target lesions (with all lymph nodes must be non-pathological in size or under 10 mm in short axis) and PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ORR= CR+PR. The ITT population included all subjects who received at least one dose of tazemetostat.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at screening (within 14 days before start of study intervention) and every 8 weeks post start of dosing, approximately up to 302 weeks

Notes:

[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: There are 8 different phases in the trial (7 dose escalation phases and the dose expansion phase with 4 cohorts) within the same period (overall study). All 8 phases are encompassed within the baseline period but the dose escalation and dose expansion phases have different end points.

End point values	Dose Escalation Level 1	Dose Escalation Level 2	Dose Escalation Level 3	Dose Escalation Level 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	6	7
Units: Percentage of participants				
number (not applicable)	0	0	0	14.3

End point values	Dose Escalation Level 5	Dose Escalation Level 6	Dose Escalation Level 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	7	
Units: Percentage of participants				
number (not applicable)	16.7	16.7	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) (dose expansion only)

End point title	Progression Free Survival (PFS) (dose expansion only) ^[7]
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End point description:

PFS was defined as the interval of time (in weeks) from the date of first dose of study drug and the earliest date of disease progression or death, from any cause defined by RECIST or RANO criteria. Disease progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including at least a 5 mm absolute increase). The presence of new lesions also constitutes to disease progression. The ITT population included all subjects who received at least one dose of tazemetostat.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at screening (within 14 days before start of study intervention) and every 8 weeks post start of dosing, approximately up to 302 weeks

Notes:

[7] - 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: There are 8 different phases in the trial (7 dose escalation phases and the dose expansion phase with 4 cohorts) within the same period (overall study). All 8 phases are encompassed within the baseline period but the dose escalation and dose expansion phases have different end points.

End point values	Dose Expansion Cohort 1	Dose Expansion Cohort 2	Dose Expansion Cohort 3	Dose Expansion Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	20	18	6
Units: weeks				
median (confidence interval 95%)	7.9 (6.0 to 24.3)	7.7 (3.4 to 8.0)	15.9 (8.0 to 21.3)	28.3 (7.9 to 145.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) (dose expansion Only)

End point title	Overall survival (OS) (dose expansion Only) ^[8]
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End point description:

Overall survival was defined as the time (in weeks) from the first dose of study drug to the date of death due to any cause. The ITT population included all subjects who received at least one dose of tazemetostat.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at screening (within 14 days before start of study intervention) and every 8 weeks post start of dosing, approximately up to 302 weeks

Notes:

[8] - 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: There are 8 different phases in the trial (7 dose escalation phases and the dose expansion phase with 4 cohorts) within the same period (overall study). All 8 phases are encompassed within the baseline period but the dose escalation and dose expansion phases have different end points.

End point values	Dose Expansion Cohort 1	Dose Expansion Cohort 2	Dose Expansion Cohort 3	Dose Expansion Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	20	18	6
Units: weeks				
median (confidence interval 95%)	21.4 (11.0 to 50.3)	14.1 (6.9 to 22.4)	41.8 (18.6 to 55.6)	103.1 (12.3 to 185.6)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs: Day 1 until earlier of either 30 days after discontinuation of study treatment or until initiation of subsequent anticancer therapy, approximately 114 weeks (dose escalation phase) and 138.7 weeks (dose expansion phase). Deaths: Day 1 up to 302 weeks

Adverse event reporting additional description:

The safety population consists of all subjects in the ITT population who had at least one post-dose safety observation recorded.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Dose Escalation Level 1
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Reporting group description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 240 mg/m² BID in continuous 28-day cycles.

Reporting group title	Dose Escalation Level 2
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Reporting group description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 300 mg/m² BID in continuous 28-day cycles.

Reporting group title	Dose Escalation Level 3
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Reporting group description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 400 mg/m² BID in continuous 28-day cycles.

Reporting group title	Dose Escalation Level 4
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Reporting group description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 520 mg/m² BID in continuous 28-day cycles.

Reporting group title	Dose Escalation Level 5
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Reporting group description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 700 mg/m² BID in continuous 28-day cycles.

Reporting group title	Dose Escalation Level 6
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Reporting group description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 900 mg/m² BID in continuous 28-day cycles.

Reporting group title	Dose Escalation Level 7
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Reporting group description:

Subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma with SS18-SSX rearrangement received oral tazemetostat 1200 mg/m² BID in continuous 28-day cycles.

Reporting group title	Dose Expansion Cohort 1
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Reporting group description:

Subjects with ATRT who participated in the dose expansion portion of the study received 1200 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles.

Reporting group title	Dose Expansion Cohort 2
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Reporting group description:

Subjects with MRT/ RTK/select tumors with rhabdoid features who participated in the dose expansion portion of the study. Subjects whose disease was without CNS involvement received 520 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles

Reporting group title	Dose Expansion Cohort 3
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Reporting group description:

Subjects with INI-negative tumors who participated in the dose expansion portion of the study. Subjects whose disease was without CNS involvement received 520 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles. Subjects whose disease had CNS involvement received 1200 mg/m² open-label, tazemetostat BID orally in continuous 28-day cycles.

Reporting group title	Dose Expansion Cohort 4
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Reporting group description:

Subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement received 800 mg/m² tazemetostat TID orally in continuous 28-day cycles.

Serious adverse events	Dose Escalation Level 1	Dose Escalation Level 2	Dose Escalation Level 3
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
number of deaths (all causes)	7	6	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Second primary malignancy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdoid tumour			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Superior vena cava syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Apnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Unintentional medical device removal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Seizure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CNS ventriculitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoid abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dose Escalation Level 4	Dose Escalation Level 5	Dose Escalation Level 6
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	4 / 6 (66.67%)
number of deaths (all causes)	4	5	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Second primary malignancy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdoid tumour			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Superior vena cava syndrome			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Apnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Unintentional medical device removal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CNS ventriculitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoid abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dose Escalation	Dose Expansion	Dose Expansion
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	Level 7	Cohort 1	Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	12 / 19 (63.16%)	10 / 20 (50.00%)
number of deaths (all causes)	7	15	18
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Second primary malignancy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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 pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdoid tumour			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Subclavian vein thrombosis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	2 / 20 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	3 / 20 (15.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Apnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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

Dyspnoea				
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0	
Pleural effusion				
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Pneumonia aspiration				
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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	
Interstitial lung disease				
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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	
Lower respiratory tract inflammation				
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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	
Lung consolidation				
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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	
Pneumonitis				
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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	
Pneumothorax				
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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	
Pulmonary embolism				

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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			
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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			
Unintentional medical device removal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Joint injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 7 (0.00%)	4 / 19 (21.05%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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

Depressed level of consciousness subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Haemorrhage intracranial subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders Visual impairment subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Constipation subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (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
Intestinal obstruction subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
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 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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

Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Melaena			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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			
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (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
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
CNS ventriculitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Laryngitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Mastoid abscess			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Otitis externa			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Tonsillitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (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
Vascular device infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Vulval abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (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
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dose Expansion Cohort 3	Dose Expansion Cohort 4	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 18 (50.00%)	3 / 6 (50.00%)	
number of deaths (all causes)	16	4	
number of deaths resulting from adverse events	0	0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdoid tumour			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Apnoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract inflammation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung consolidation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Unintentional medical device removal			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seizure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhage intracranial subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 18 (5.56%) 1 / 1 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	
Eye disorders Visual impairment subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 18 (5.56%) 0 / 1 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 18 (0.00%) 0 / 0 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	
Constipation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 18 (0.00%) 0 / 0 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	
Intestinal obstruction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 18 (0.00%) 0 / 0 0 / 0	1 / 6 (16.67%) 0 / 1 0 / 0	
Vomiting subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 18 (0.00%) 0 / 0 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	
Diarrhoea subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 18 (5.56%) 1 / 1 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	
Dysphagia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 18 (0.00%) 0 / 0 0 / 0	0 / 6 (0.00%) 0 / 0 0 / 0	

Melaena			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (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			
Urinary tract obstruction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (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 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (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 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CNS ventriculitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoid abscess			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (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	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dose Escalation Level 1	Dose Escalation Level 2	Dose Escalation Level 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	5 / 6 (83.33%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0

Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	3
Melanocytic naevus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peritumoural oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tumour haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis limb			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	0	3	3
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Catheter site swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 2	0 / 6 (0.00%) 0
Catheter site pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Axillary pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Catheter site erosion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Generalised oedema subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Reproductive system and breast disorders Vulvovaginal rash subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Breast pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Dysmenorrhoea			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Menstruation irregular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	4	1
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Hypoxia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Tachypnoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Atelectasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphonia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lung consolidation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stridor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Yawning			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Increased bronchial secretion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumothorax			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wheezing			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Psychiatric disorders			
Irritability			
subjects affected / exposed	3 / 8 (37.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Behaviour disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fear			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Euphoric mood			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Mental disorder subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Mental status changes subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Nightmare subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Investigations			
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 3	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood bromide increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Bacterial test positive subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 4
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood creatinine increased			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
White blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Skin laceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Spinal fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Left ventricular dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Defect conduction intraventricula			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 8 (0.00%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	0	2	3
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Dysmetria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Auditory nerve disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Facial nerve disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Facial paresis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
IIIrd nerve paralysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
IVth nerve paralysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
VIth nerve paralysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Drooling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhage intracranial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hemiparesis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ataxia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuromyopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sensory loss			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
VIth nerve disorder			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	3	1	2
Lymphopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophilia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Motion sickness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tympanic membrane perforation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
External ear inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Deafness transitory			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eyelid function disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Conjunctivitis allergic subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Corneal epithelium defect subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Exophthalmos subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Gaze palsy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Neurotrophic keratopathy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Papilloedema subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Photophobia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	2 / 6 (33.33%) 3	3 / 6 (50.00%) 5
Nausea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 6 (33.33%) 2	3 / 6 (50.00%) 6
Constipation subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	2 / 6 (33.33%) 2	3 / 6 (50.00%) 4
Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 3	0 / 6 (0.00%) 0
Abdominal pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Chapped lips			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lip blister			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Teething			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cheilitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Duodenal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tongue erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth development disorder			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cholestasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatocellular injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blister			

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hair texture abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Onychoclasia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Scab			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis bullous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Telangiectasia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urine odour abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Acute kidney injury subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Facial asymmetry subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Joint range of motion decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Muscular weakness			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fracture pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Candida infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mucosal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Tinea pedis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Rhinovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin candida			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Body tinea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Coronavirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Enterovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection pseudomonal subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	2 / 6 (33.33%) 2
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2
Hypophosphataemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Hypermagnesaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 3
Hyponatraemia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Dehydration subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Hyperchloraemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Hyperkalaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Dose Escalation Level 4	Dose Escalation Level 5	Dose Escalation Level 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	4	3	0
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Melanocytic naevus			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin papilloma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peritumoural oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tumour haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lymphoedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis limb			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	1	2	3
Pyrexia			

subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	2	5	4
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Catheter site swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Feeling cold			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Catheter site pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Catheter site erosion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Generalised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Vulvovaginal rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Breast pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Menstruation irregular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 7 (0.00%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	0	5	9
Nasal congestion			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	3
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Atelectasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	2
Interstitial lung disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lung consolidation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stridor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Yawning			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Increased bronchial secretion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Irritability			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Restlessness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Behaviour disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fear			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Euphoric mood			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mental disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Mental status changes subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Nightmare subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Investigations			
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 5	0 / 6 (0.00%) 0	3 / 6 (50.00%) 6
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Weight decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood bromide increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Bacterial test positive subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 4	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Weight increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fracture			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Spinal fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Left ventricular dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Defect conduction intraventricula			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	3	2
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysmetria			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Auditory nerve disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Facial nerve disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Facial paresis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
IIIrd nerve paralysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
IVth nerve paralysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
VIth nerve paralysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Drooling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhage intracranial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hemiparesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ataxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuromyopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sensory loss			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
VIth nerve disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	3
Lymphopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neutrophilia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ear discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	3
Motion sickness			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypoacusis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
External ear inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Deafness transitory			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eyelid function disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Corneal epithelium defect subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Exophthalmos subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Gaze palsy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Neurotrophic keratopathy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Papilloedema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Photophobia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 4	3 / 6 (50.00%) 7	2 / 6 (33.33%) 4
Nausea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	3 / 6 (50.00%) 5	2 / 6 (33.33%) 3
Constipation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1
Diarrhoea subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3	4 / 6 (66.67%) 6	2 / 6 (33.33%) 6
Abdominal pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	3 / 6 (50.00%) 4	1 / 6 (16.67%) 2
Stomatitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Chapped lips			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lip blister			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Teething			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphagia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Duodenal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tongue erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth development disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cholestasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatocellular injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Onychoclasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Rash erythematous			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin lesion			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis bullous			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Telangiectasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Urine odour abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Facial asymmetry			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fracture pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	9	1	2
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	5
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Hordeolum			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Mucosal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Otitis media acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Viral rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Skin candida			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Body tinea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Coronavirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Enterovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Hypermagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperchloraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Hyperuricaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Dose Escalation Level 7	Dose Expansion Cohort 1	Dose Expansion Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	19 / 19 (100.00%)	19 / 20 (95.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	2 / 20 (10.00%)
occurrences (all)	0	3	2
Melanocytic naevus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Peritumoural oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tumour haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	3 / 20 (15.00%)
occurrences (all)	1	1	3
Embolism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Lymphoedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis limb			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	4 / 19 (21.05%)	2 / 20 (10.00%)
occurrences (all)	1	4	2
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	4 / 19 (21.05%)	5 / 20 (25.00%)
occurrences (all)	1	6	8
Oedema peripheral			

subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Catheter site swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Feeling cold			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Catheter site pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Axillary pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Catheter site erosion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Generalised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vulvovaginal rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Breast pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Menstruation irregular			

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 7 (28.57%)	6 / 19 (31.58%)	4 / 20 (20.00%)
occurrences (all)	2	11	5
Nasal congestion			
subjects affected / exposed	2 / 7 (28.57%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	2	2	1
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	2	2
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	3
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Atelectasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Productive cough			

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Interstitial lung disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Lung consolidation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Stridor			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Yawning			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Increased bronchial secretion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	2	2	1

Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Behaviour disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Fear			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Delirium			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Euphoric mood			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Mental disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Mental status changes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Nightmare subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Investigations			
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 19 (5.26%) 4	2 / 20 (10.00%) 7
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 19 (10.53%) 3	1 / 20 (5.00%) 1
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 19 (10.53%) 4	3 / 20 (15.00%) 3
Weight decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 19 (5.26%) 1	3 / 20 (15.00%) 3
Blood bromide increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 19 (10.53%) 3	1 / 20 (5.00%) 1
Bacterial test positive subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 19 (10.53%) 2	1 / 20 (5.00%) 1
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 19 (0.00%) 0	1 / 20 (5.00%) 3
Weight increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1
White blood cell count decreased			

subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Arthropod sting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Spinal fracture			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	2	1	2
Left ventricular dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Defect conduction intraventricula			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 7 (14.29%)	4 / 19 (21.05%)	1 / 20 (5.00%)
occurrences (all)	1	6	1
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dysmetria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Auditory nerve disorder			

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Facial nerve disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Facial paresis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
IIIrd nerve paralysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
IVth nerve paralysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
VIth nerve paralysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Drizzling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Dyskinesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Haemorrhage intracranial			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hemiparesis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Ataxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Neuromyopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Sensory loss			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
VIth nerve disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 19 (21.05%)	8 / 20 (40.00%)
occurrences (all)	4	29	18

Lymphopenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	3	1	0
Thrombocytopenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	4	1	0
Leukopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Neutrophilia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Motion sickness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane perforation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
External ear inflammation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Otorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Deafness transitory			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Eyelid function disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Corneal epithelium defect			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

Exophthalmos			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gaze palsy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Neurotrophic keratopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Papilloedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 7 (85.71%)	11 / 19 (57.89%)	9 / 20 (45.00%)
occurrences (all)	12	19	14
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	6 / 19 (31.58%)	5 / 20 (25.00%)
occurrences (all)	1	6	5
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	4 / 20 (20.00%)
occurrences (all)	1	2	4
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	7 / 19 (36.84%)	3 / 20 (15.00%)
occurrences (all)	1	12	3
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	4 / 20 (20.00%)
occurrences (all)	0	1	4
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Abdominal distension			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Chapped lips			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Lip blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Teething			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Cheilitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Duodenal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Melaena			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tongue erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tooth development disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			

Hepatitis toxic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cholestasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hepatocellular injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	2 / 20 (10.00%)
occurrences (all)	1	2	2
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	3 / 20 (15.00%)
occurrences (all)	0	1	3
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin hyperpigmentation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Onychoclasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Scab			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Acne			

subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dermatitis bullous			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Telangiectasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Urine odour abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 19 (5.26%) 2	2 / 20 (10.00%) 2
Facial asymmetry subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 19 (5.26%) 2	0 / 20 (0.00%) 0
Joint range of motion decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Muscular weakness subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Neck pain			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Fracture pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Groin pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	3 / 19 (15.79%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	1	3	1
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	4	2
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Lower respiratory tract infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Mucosal infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0
Otitis externa subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 19 (5.26%) 5	0 / 20 (0.00%) 0
Otitis media acute subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1
Pneumonia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	2 / 20 (10.00%) 3
Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Skin infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1
Tinea pedis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0
Viral rash subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 19 (0.00%) 0	0 / 20 (0.00%) 0

Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Fungal skin infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	4	0
Impetigo			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Rhinovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Skin candida			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Viral rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Body tinea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Coronavirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Enterovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 7 (14.29%)	5 / 19 (26.32%)	4 / 20 (20.00%)
occurrences (all)	1	5	4
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 19 (15.79%)	2 / 20 (10.00%)
occurrences (all)	0	5	2
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	4	1
Hypermagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	2 / 20 (10.00%)
occurrences (all)	0	4	2
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hyperchloraemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			

subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Dose Expansion Cohort 3	Dose Expansion Cohort 4	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)	6 / 6 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Tumour pain			
subjects affected / exposed	3 / 18 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Melanocytic naevus			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin papilloma			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Peritumoural oedema			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tumour haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 18 (11.11%)	1 / 6 (16.67%)	
occurrences (all)	3	3	
Embolism			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Venous thrombosis limb			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 18 (27.78%)	2 / 6 (33.33%)	
occurrences (all)	7	3	
Pyrexia			
subjects affected / exposed	7 / 18 (38.89%)	0 / 6 (0.00%)	
occurrences (all)	16	0	
Oedema peripheral			
subjects affected / exposed	5 / 18 (27.78%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Asthenia			

subjects affected / exposed	1 / 18 (5.56%)	3 / 6 (50.00%)
occurrences (all)	1	3
Gait disturbance		
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Catheter site swelling		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Chest pain		
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)
occurrences (all)	1	1
Chills		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Face oedema		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Feeling cold		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Localised oedema		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Malaise		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Non-cardiac chest pain		
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)
occurrences (all)	1	1
Catheter site pain		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Influenza like illness		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Axillary pain		

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 6 (16.67%) 1	
Catheter site erosion subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Generalised oedema subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 6 (16.67%) 1	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Reproductive system and breast disorders Vulvovaginal rash subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Breast pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 6 (16.67%) 1	
Menorrhagia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	0 / 6 (0.00%) 0	
Menstruation irregular subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 6 (16.67%) 2	
Respiratory, thoracic and mediastinal disorders			

Cough		
subjects affected / exposed	6 / 18 (33.33%)	3 / 6 (50.00%)
occurrences (all)	8	4
Nasal congestion		
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)
occurrences (all)	2	0
Dyspnoea		
subjects affected / exposed	0 / 18 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	4
Hypoxia		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	3	0
Oropharyngeal pain		
subjects affected / exposed	3 / 18 (16.67%)	1 / 6 (16.67%)
occurrences (all)	4	1
Pleural effusion		
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Tachypnoea		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Atelectasis		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Dysphonia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Epistaxis		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Productive cough		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Rales		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0

Rhinitis allergic			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Interstitial lung disease			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Lung consolidation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Stridor			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Yawning			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Increased bronchial secretion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pneumothorax			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Anxiety			

subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Restlessness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Behaviour disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Fear			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Agitation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Delirium			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Euphoric mood			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Mental disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Mental status changes			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Investigations			

Platelet count decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Weight decreased			
subjects affected / exposed	0 / 18 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	8	
Blood bromide increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Bacterial test positive			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Blood creatinine increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Weight increased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
White blood cell count decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 6 (16.67%) 1	
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 6 (16.67%) 1	
C-reactive protein increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Skin laceration subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Skin abrasion subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Ligament sprain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	
Arthropod sting subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	
Fracture subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	
Spinal fracture subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	
Cardiac disorders			

Sinus tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Left ventricular dysfunction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Defect conduction intraventricula			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Sinus bradycardia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 18 (38.89%)	3 / 6 (50.00%)	
occurrences (all)	9	3	
Dizziness			
subjects affected / exposed	2 / 18 (11.11%)	1 / 6 (16.67%)	
occurrences (all)	2	2	
Paraesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dysmetria			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Auditory nerve disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Facial nerve disorder			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Facial paresis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
IIIrd nerve paralysis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
IVth nerve paralysis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Lethargy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
VIth nerve paralysis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Disturbance in attention			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Drooling			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Dyskinesia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Haemorrhage intracranial			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hemiparesis			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Ataxia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hyperaesthesia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Neuralgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neuromyopathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Sensory loss			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
VIth nerve disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 18 (27.78%)	0 / 6 (0.00%)	
occurrences (all)	13	0	
Lymphopenia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	10	

Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 6 (33.33%)	
occurrences (all)	1	7	
Leukopenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neutrophilia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Leukocytosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Ear discomfort			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Ear pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Motion sickness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Tympanic membrane perforation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypoacusis			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
External ear inflammation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Otorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Deafness transitory			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Deafness unilateral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Eyelid function disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis allergic			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Corneal epithelium defect			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Exophthalmos			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Gaze palsy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Neurotrophic keratopathy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Papilloedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	11 / 18 (61.11%)	5 / 6 (83.33%)	
occurrences (all)	34	19	
Nausea			
subjects affected / exposed	11 / 18 (61.11%)	3 / 6 (50.00%)	
occurrences (all)	16	3	
Constipation			
subjects affected / exposed	3 / 18 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	3	2	
Diarrhoea			
subjects affected / exposed	7 / 18 (38.89%)	2 / 6 (33.33%)	
occurrences (all)	11	4	
Abdominal pain			
subjects affected / exposed	3 / 18 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Stomatitis			
subjects affected / exposed	3 / 18 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Abdominal distension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			

subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Chapped lips		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Dyspepsia		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Flatulence		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Gastritis		
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Lip blister		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Rectal haemorrhage		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Teething		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Cheilitis		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Dysphagia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Haemorrhoids		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Abdominal discomfort		

subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Duodenal obstruction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Haematemesis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Melaena			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Mouth ulceration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Odynophagia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oesophagitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tongue erythema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tooth development disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Cholestasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hepatocellular injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Jaundice			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Alopecia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Blister			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hyperhidrosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin hyperpigmentation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	2	0
Hair texture abnormal		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Onychoclasia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Rash		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Rash erythematous		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Rash macular		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Rash papular		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Urticaria		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	4	0
Dermatitis diaper		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Scab		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Skin lesion		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Acne		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Dermatitis bullous		

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dermatitis contact			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Eczema			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nail disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Telangiectasia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Urine odour abnormal			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Acute kidney injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	0 / 18 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Nephrolithiasis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 18 (22.22%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Facial asymmetry			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Joint range of motion decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Muscular weakness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Bone pain			

subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Fracture pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Groin pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Otitis media			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 18 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Rhinitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hordeolum			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Mucosal infection		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Otitis externa		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Otitis media acute		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Pharyngitis		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Pharyngitis streptococcal		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Pneumonia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Respiratory tract infection viral		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Sinusitis		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Skin infection		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Tinea pedis		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Viral rash		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Viral upper respiratory tract infection		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0

Conjunctivitis		
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Escherichia urinary tract infection		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Fungal skin infection		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Herpes simplex		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Impetigo		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Nasopharyngitis		
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)
occurrences (all)	1	1
Parainfluenzae virus infection		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Pneumonia pneumococcal		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Respiratory syncytial virus infection		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Rhinovirus infection		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Skin candida		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Viral infection		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0

Viral rhinitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Body tinea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
COVID-19			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Coronavirus infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Device related infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Enterovirus infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 18 (22.22%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Hypokalaemia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	2
Hypertriglyceridaemia		
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)
occurrences (all)	3	0
Hypophosphataemia		
subjects affected / exposed	1 / 18 (5.56%)	2 / 6 (33.33%)
occurrences (all)	1	2
Hypermagnesaemia		
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)
occurrences (all)	1	1
Hypoalbuminaemia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Hyponatraemia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Dehydration		
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Hyperchloraemia		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	1	0
Hyperglycaemia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Hyperkalaemia		
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)
occurrences (all)	2	0
Hyperuricaemia		
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0
Hypomagnesaemia		
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Hypercalcaemia		

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypoglycaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vitamin D deficiency			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypernatraemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2015	Original Protocol submitted to FDA, never submitted to sites.
24 August 2015	Amendment v1.0 – submitted to all sites. Key changes: <ul style="list-style-type: none">- Added a dose level to start at a lower dose (240mg/m² vs. original 300mg/m²) and effectively increasing the dose escalation phase numbers from 18 to 24 subjects.- Additional details on blood sampling volumes added.- Removed mandatory requirement to collect date of birth.
02 October 2015	Amendment v2.0 – submitted to all sites. Key changes: <ul style="list-style-type: none">- Added selected tumors with rhabdoid features that responses were seen in Phase 1 (SMARCA4 loss in MRT0 or SCCOHT).- Removed requirement for fasting based upon data in food-effect study.- Removed restriction for pregnancy prevention 30 days prior to entry.
12 October 2015	Amendment v2.1 – Country-specific for Germany Key changes: <ul style="list-style-type: none">- Upper age limit changes to <12 years old due to inability to do Panorex films in Germany (radiation exposure an issue).- Removed MUGA scan as it is not performed in Germany.- Removed bone monitoring and Karnofsky performance due to age change.
03 December 2015	Amendment v2.2 – Country-specific for United Kingdom Key changes: <ul style="list-style-type: none">- Lower age limit increased to >1 year old (vs. 6 mos for rest of world).- No subjects <5 years old in UK will be enrolled until 4 subjects study wide have received at least 4 weeks of study drug.- Pregnancy prevention in females and males updated to reflect UK law.
31 March 2016	Amendment v2.3 – Country-specific for Germany Key changes: <ul style="list-style-type: none">- Removal of synovial and other INI1-negative/SMARCA4 negative tumors
11 May 2016	Amendment v3.0 – submitted to all sites. Key changes: <ul style="list-style-type: none">- Changes to include treated brain mets.- Remove Panorex.- Remove baseline visit and other changes made to 202.- Add cohorts - Cohort 1: atypical teratoid rhabdoid tumor (ATRT), Cohort 2: non-ATRT rhabdoid tumors and Cohort 3: INI1-negative tumors or synovial sarcoma.
22 June 2016	Amendment v3.1 – Country-specific for Germany Key changes: <ul style="list-style-type: none">- Incorporating all changes from amendment v3.0

13 July 2016	Amendment v3.2 – Country-specific for United Kingdom Key changes: - Incorporating all changes from amendment v3.0
27 July 2016	Amendment v4.0 – submitted to all sites Key changes: - Four dose expansion levels added. - Number of subjects changed from 84 to 108. - Allow replacement of subjects who discontinue in absence of a dose-limiting toxicity [DLT] prior to the completing of the DLT evaluation period.
02 August 2016	Amendment v4.1 – Country-specific for Germany Key changes: - All changes from v4.0 incorporated
21 October 2016	Amendment v4.3 – Country-specific for United Kingdom Key changes: - All changes from v4.0 incorporated
20 July 2017	Amendment v5.0 – submitted to all sites Key changes: - RP2D was determined to be 1200 mg/m ² BID and will be used in the dose expansion portion of the study. - New cohort 4 added for subjects ≥10 years to ≤21 years to receive tazemetostat tablets. - Number of subjects changed from 108 to 120. - Information on hydrobromide salt, hyperchloremia and potential associated toxicities added. - Cycle length and study procedure timings changed for Cycles 13 and beyond to 21 days.
26 July 2017	Amendment v5.3 – Country-specific for United Kingdom Key changes: - Tablet formulation cohort added; this cohort (Cohort 4) will not enroll subjects in Germany - The RP2D was determined to be 1200 mg/m ² BID and will be the dose used in the dose expansion portion of the study - New cohort added to Dose Expansion phase of study (outside of Germany): Cohort 4 to received tazemetostat tablets 800 mg/m ² TID [2400 mg/m ² /day]); Subjects are to be ≥10 years to ≤21 years with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement and able to swallow tablets) - Information on hydrobromide salt, hyperchloremia, and potential associated toxicities had been added; also, bromide measurements have been added - Number of subjects increased from 108 to 120 - Additional preliminary PK data added - Additional prohibited medications added - Cycle length for Cycles 13 and beyond changed to 21 days. - Study procedure timings updated for Cycles 13 and beyond to reflect 21-day cycle - Dose modification information has been updated - Expansion of requirements for additional biopsies for subjects who progress to include all subjects (including SD) not just subjects who experienced PR or better. - Safety section has been updated - New appendix added for Cohort 4 dosing and dose modification - Minor corrections

03 August 2017	<p>Amendment v5.1 – Country-specific for Germany</p> <p>Key changes:</p> <ul style="list-style-type: none"> - Tablet formulation cohort added; this cohort (Cohort 4) will not enroll subjects in Germany - The RP2D was determined to be 1200 mg/m² BID and will be the dose used in the dose expansion portion of the study - New cohort added to Dose Expansion phase of study (outside of Germany): Cohort 4 to received tazemetostat tablets 800 mg/m² TID [2400 mg/m²/day]); Subjects are to be ≥10 years to ≤21 years with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement and able to swallow tablets) - Information on hydrobromide salt, hyperchloremia, and potential associated toxicities had been added; also, bromide measurements have been added - Number of subjects increased from 108 to 120 - Additional preliminary PK data added - Additional prohibited medications added - Cycle length for Cycles 13 and beyond changed to 21 days. - Study procedure timings updated for Cycles 13 and beyond to reflect 21-day cycle - Dose modification information has been updated - Expansion of requirements for additional biopsies for subjects who progress to include all subjects (including SD) not just subjects who experienced PR or better. - Safety section has been updated - New appendix added for Cohort 4 dosing and dose modification - Minor corrections
31 October 2017	<p>Amendment v5.4 – Country-specific for France</p> <p>Key changes:</p> <ul style="list-style-type: none"> - Updated text on phototoxicity. - Updated text to clarify chloride levels are assessed at every visit locally and centrally and bromide levels will be analyzed centrally. - Added additional prohibited meds. - Removed PD samples at C13 and beyond. - Correct inconsistency in Exclusion criteria #11 in two different sections of the protocol. - Remove PD blood sample collection from procedures and assessments conducted at Cycle 13 and beyond. Add language about stopping PD sample collection after 20 evaluable PD samples are collected through Day 15 upon Sponsor notification. - Minor corrections
01 February 2018	<p>Amendment v5.5 – Country-specific for France</p> <p>Key changes:</p> <ul style="list-style-type: none"> - Option to change from suspension to tablets
28 September 2018	<p>Amendment v6.0 – submitted to all sites</p> <p>Key changes:</p> <ul style="list-style-type: none"> - All changes from v5.5 - Updated with 2 new AESIs – T-LBL/T-ALL and MDS. - Added exclusion criteria to exclude patients with thrombocytopenia, neutropenia, anemia of Grade ≥3 and history of MDS and T-LBL and MDS. - Hold treatment to either modify or discontinue if patient develop MDS/AML. - Patients have a maximum of cumulative 2 years on the study. - Updated dose modification or discontinuation section. - Changed age from ≤21 years to <18 years. - Addition of assessments – blood smear morphology and annual PK. - Removed Cycle 13 and beyond study design. - Allow patients to change to tablet dosing after completion of Cycle 1

10 October 2018	Amendment v6.2 – Country-specific for United Kingdom - All changes from v6.0 incorporated
07 November 2018	Amendment v6.1 – Country-specific for Germany - All changes from v6.0 incorporated
13 December 2018	Amendment v7.2 – Country-specific for United Kingdom - All changes from v7.0 incorporated
17 December 2018	Amendment v7.0 – submitted to all sites. Key changes: - Addition of the option to discontinue treatment if the Investigator determines the dose of tazemetostat must be modified for subjects enrolled in the dose expansion part of the study. - Alignment of the disease assessment frequency of bone scans with the RECIST guidelines in Appendix 4. - Update of dose rationale language with the starting dose of 520 mg/m ² BID for newly enrolled subjects with non-ATRT tumors to align with the new dosing requirements. - Cohort 1 enrollment has been closed as there has been sufficient data collected in pediatric subjects with ATRT. - Cohort 4 enrollment has been closed as there has been sufficient pharmacokinetic data collected in pediatric subjects who were administered tazemetostat in tablet form. - Removal of language allowing subjects who do not have clinical or radiographic disease progression and do not experience unacceptable toxicity to receive tazemetostat beyond cycle 1. Removal of language allowing subjects who have modest disease progression in the absence of clinical deterioration to remain on study. - Addition of the definition of adverse drug reaction to the overall definitions section. - Addition of the definition of a suspected unexpected serious adverse reaction (SUSAR) to the overall definitions section. - Addition of safety language to suggest that rapid communication of adverse events of special interest should be communicated to the Sponsor to allow the event to be understood and characterized in a timely manner. - Removal of dose escalation from interim analysis section of the statistical analysis plan, as this was added in error. - Change in the confidence interval from 90% to 95% when calculating overall survival, and from 80% to 95% when calculating objective response rate.
15 March 2019	Amendment v6.3 – Country-specific for Germany Key changes: - Removal of the option of tablet dosing as dose reduction, if needed, is not possible with the tablet formulations currently in use. - Removal of the requirement of Karnofsky Performance Status >50% for subjects ≥12 years of age as all subjects in Germany are <12 years of age upon enrollment, and the Lansky Performance Scale is used for subjects <12 years of age. - Removal of the requirement specific to French subjects, that they be affiliated with or a beneficiary or a social security category, as this protocol only applies to subjects in Germany. - Removal of the requirement of SMARCA4 loss from IHC or molecular confirmation of SMARCA4 loss as this gene is associated with SCCOHT tumors, which will not be studied in Germany. - Removal of the requirement for subjects enrolled in cohort 4 (not open in Germany) to be able to swallow tablets as tablet dosing options will no longer be permitted. - Removal of language stating that for subjects who have modest disease progression in the absence of clinical deterioration and are receiving clinical benefit in the opinion of the Investigator, the Investigator should contact the Medical Monitor to discuss keeping the subject on study as subjects must come off study in the event of disease progression.

20 February 2020	<p>Amendment v8.0 – submitted to all sites.</p> <p>Key changes:</p> <ul style="list-style-type: none"> - Updated the study period to reflect the first subject's first visit and current projections for last subject last visit. - Updated the anticipated safety profile to align with the current IB. - Included T-LBL/T-ALL with other events that will trigger convening of safety committees and to clarify that consequences of an event of T-LBL/T-ALL will occur regardless of dose level. - Modified dose modification text to state that for MDS, AML or any myeloid malignancy like MPN, tazemetostat will be discontinued. - Removed dose modification sub-section for dose modifications due to MDS. - Adjusted and clarified dose modifications for subjects in dose expansion starting at 1200mg/m2 and for subjects starting at 520mg/m2. - Removed blood chemistry collection at Day 15 of Cycles 2 and beyond to reduce the amount of blood drawn for unnecessary testing. - Modified requirement for the timing of screening disease assessments to allow for assessments done more than 14 days before enrollment. - Updated contraception requirements to reflect current expectations and to align with approved labeling in the US. - Added genitourinary exam to comprehensive physical exam to ensure abnormalities and malignancies are not missed. - Specified that elevated bromide is considered an event of clinical interest, and that events of clinical interest are to be reported in the same manner as SAEs. - Corrected the confidence interval from 90% to 95% to be estimated in the case of sufficient number of deaths to trigger survival endpoint assessments by Brookmeyer-Crowley.
03 April 2020	<p>Amendment v8.2 – Country-specific for United Kingdom</p> <ul style="list-style-type: none"> - All changed from v8.0 incorporated
03 April 2020	<p>Amendment v8.3 – Country-specific for Germany</p> <ul style="list-style-type: none"> - All changed from v8.0 incorporated
01 July 2020	<p>Amendment v8.4 – Country-specific for Germany</p> <p>Key changes:</p> <ul style="list-style-type: none"> - Clarification of the roles of existing safety committees. - Corrected an inaccuracy in wording that was made to clarify that if enrollment of new patients is suspended in the event of a new case of T-LBL/T-ALL, patients on study who continue to derive clinical benefit "may" (rather than "will") be maintained on therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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06 April 2018	<p>On 06 April 2018, an event of T-LBL was observed in a pediatric subject on study EZH-102.</p> <p>The SUSAR of T-LBL resulted in the Sponsor initiating a temporary global halt in enrollment for the pediatric study EZH-102. In addition, this event led to a partial clinical hold (PCH) on new subject enrollment for tazemetostat by the U.S. (FDA), France (ANSM), and Germany (BfArM) across all studies of the Tazemetostat Development Program.</p> <p>Following this report, Epizyme conducted a comprehensive evaluation. Based on this evaluation, we continued to believe that tazemetostat is a clinically active drug and has the potential to benefit both adult and pediatric patients across different tumor types where there are unmet medical needs. We also concluded that the risk assessment identifies a possible direct association between tazemetostat and T-LBL/T-ALL. Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients based on 1) higher AUC0-24h exposures in pediatric patients, 2) increases over time in age-related thymic involution, and 3) the known epidemiology/pathophysiology of T-LBL/ALL. The risk of T-LBL/T-ALL in adults is not known, however the incidence of treatment-related T-LBL/T-ALL in adults is expected to be uncommon.</p> <p>Heightened surveillance was and continues to be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of T-LBL/T-ALL so that tazemetostat may be discontinued in the subject and treatment can be initiated for these malignancies. If a case of adult T-LBL/T-ALL occurs, enrollment will be suspended and the benefit-risk of the drug will be assessed by the Tazemetostat Safety Committee and will be communicated to all Health Authorities and Ethics Committees.</p> <p>To date, no adult T-LBL/T-ALL cases have occurred.</p>	28 September 2018
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Notes:

Limitations and caveats

None reported