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	v1
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	EZH-102

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)	EMEA-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?	Yes
Primary completion date	19 June 2021
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 MTD or the RP2D of tazemetostat when administered as an oral suspension BID in pediatric subjects with relapsed/refractory rhabdoid tumors, 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	Efficacy, Safety
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:

240 mg/m2 BID (starting dose) = 480 mg/m2/day

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 2

Arm description:

300 mg/m2 BID = 600 mg/m2/day

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 3

Arm description:

400 mg/m2 BID = 800 mg/m2/day

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 4

Arm description:

520 mg/m2 BID = 1040 mg/m2/day

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

Arm description:

700 mg/m2 BID = 1400 mg/m2/day

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

Arm description:

900 mg/m2 BID = 1800 mg/m2/day

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

Arm description:

1200 mg/m2 BID = 2400 mg/m2/day

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 Expansion Cohort 1

Arm description:

Subjects with ATRT

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 Expansion Cohort 2

Arm description:

Subjects with malignant rhabdoid tumor (MRT)/ rhabdoid tumor of kidney (RTK)/select tumors with rhabdoid features

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 Expansion Cohort 3

Arm description:

Subjects with INI1-negative tumors

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 Expansion Cohort 4

Arm description:

Subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement

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
Consent withdrawn by subject	1	-	-
Physician decision	-	-	-
death	-	-	-
unknown	-	-	-
Adverse event, non-fatal	-	-	-
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
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
death	-	-	-
unknown	-	-	-
Adverse event, non-fatal	-	-	1
Unacceptable toxicity	-	-	-
Disease Progression	6	6	4

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
Consent withdrawn by subject	1	2	-
Physician decision	-	-	-
death	-	-	1

unknown	-	-	2
Adverse event, non-fatal	-	-	-
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
Consent withdrawn by subject	-	-
Physician decision	1	1
death	-	-
unknown	2	-
Adverse event, non-fatal	1	-
Unacceptable toxicity	-	-
Disease Progression	14	4

Baseline characteristics

Reporting groups	
Reporting group title	Dose Escalation Level 1
Reporting group description:	
240 mg/m2 BID (starting dose) = 480 mg/m2/day	
Reporting group title	Dose Escalation Level 2
Reporting group description:	
300 mg/m2 BID = 600 mg/m2/day	
Reporting group title	Dose Escalation Level 3
Reporting group description:	
400 mg/m2 BID = 800 mg/m2/day	
Reporting group title	Dose Escalation Level 4
Reporting group description:	
520 mg/m2 BID = 1040 mg/m2/day	
Reporting group title	Dose Escalation Level 5
Reporting group description:	
700 mg/m2 BID = 1400 mg/m2/day	
Reporting group title	Dose Escalation Level 6
Reporting group description:	
900 mg/m2 BID = 1800 mg/m2/day	
Reporting group title	Dose Escalation Level 7
Reporting group description:	
1200 mg/m2 BID = 2400 mg/m2/day	
Reporting group title	Dose Expansion Cohort 1
Reporting group description:	
Subjects with ATRT	
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	
Reporting group title	Dose Expansion Cohort 3
Reporting group description:	
Subjects with INI1-negative tumors	
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	

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

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

Reporting group values	Dose Escalation Level 7	Dose Expansion Cohort 1	Dose Expansion 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

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

End points

End points reporting groups

Reporting group title	Dose Escalation Level 1
Reporting group description: 240 mg/m2 BID (starting dose) = 480 mg/m2/day	
Reporting group title	Dose Escalation Level 2
Reporting group description: 300 mg/m2 BID = 600 mg/m2/day	
Reporting group title	Dose Escalation Level 3
Reporting group description: 400 mg/m2 BID = 800 mg/m2/day	
Reporting group title	Dose Escalation Level 4
Reporting group description: 520 mg/m2 BID = 1040 mg/m2/day	
Reporting group title	Dose Escalation Level 5
Reporting group description: 700 mg/m2 BID = 1400 mg/m2/day	
Reporting group title	Dose Escalation Level 6
Reporting group description: 900 mg/m2 BID = 1800 mg/m2/day	
Reporting group title	Dose Escalation Level 7
Reporting group description: 1200 mg/m2 BID = 2400 mg/m2/day	
Reporting group title	Dose Expansion Cohort 1
Reporting group description: Subjects with ATRT	
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	
Reporting group title	Dose Expansion Cohort 3
Reporting group description: Subjects with INI1-negative tumors	
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	

Primary: Dose limiting toxicities (DLTs)

End point title	Dose limiting toxicities (DLTs)[1][2]

End point description:

A DLT is a significant adverse reaction (with the exception of tumor progression) that meets any of the following criteria:

- Non-hematologic toxicity: any other Grade 3 or greater non-hematologic toxicity except:
- alopecia
- fatigue/asthenia
- transient myalgia/arthralgia
- Grade 3 vomiting or diarrhea that resolves to ≤Grade 2 within 48 hours (with or without supportive care)
- Grade 3 nausea that resolves (with or without supportive care) to ≤Grade 2 within 7 days

- Grade 3 anorexia requiring enteral or parenteral nutrition
- Hematologic toxicity: myelosuppression, defined as:
- Grade 4 thrombocytopenia of any duration, or Grade 3 thrombocytopenia with bleeding or lasting >7 days
- Grade 4 neutropenia for five consecutive days.
- Treatment delay of more than 14 days due to delayed recovery from a toxicity related to treatment with tazemetostat

End point type	Primary

End point timeframe:

A DLT was determined in the first treatment cycle only (Day 1 to Day 28) of dose escalation. From the start of study treatment until the end of the first cycle (Day 28) of treatment.
It was graded according to the CTCAE version 4.03.

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	8	6	6	7
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	7	
Units: number	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR)[3][4]

End point description:

ORR is defined as the percentage of subjects achieving a confirmed complete response (CR) or partial response (PR) from the start of treatment until disease progression or the start of new anticancer therapy, whichever occurs first.

End point type	Primary

End point timeframe:

From start of treatment until disease progression or the start of new anticancer therapy, whichever occurs first.

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: Number of objective responders	5	0	3	1

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)[5]

End point description:

ORR is defined as the percentage of subjects achieving a confirmed complete response (CR) or partial response (PR) from the start of treatment until disease progression or the start of new anticancer therapy, whichever occurs first.

End point type	Secondary

End point timeframe:

From start of treatment until disease progression or the start of new anticancer therapy, whichever occurs first.

Notes:

[5] - 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: Number of objective responders	0	0	0	1

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: Number of objective responders	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[6]

End point description:

The PFS is 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.

End point type	Secondary

End point timeframe:

From first dose of study drug until the earliest date of disease progression or death, from any cause.

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 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: Number of patients				
median (confidence interval 95%)	7.9 (6.0 to 24.3)	7.7 (3.4 to 8)	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)

End point title	Overall survival (OS)[7]

End point description:

The OS is defined as the interval of time (in weeks) between the date of first dose of study drug and the date of death from any cause.

End point type	Secondary

End point timeframe:

From first dose of study drug until the earliest date of death from any cause.

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: Number of patients				
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:

Adverse event monitoring starts from the time the patient consents to the study until they complete the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Dose Escalation Level 1
Reporting group description:	
240 mg/m2 BID (starting dose) = 480 mg/m2/day	
Reporting group title	Dose Escalation Level 2
Reporting group description:	
300 mg/m2 BID = 600 mg/m2/day	
Reporting group title	Dose Escalation Level 3
Reporting group description:	
400 mg/m2 BID = 800 mg/m2/day	
Reporting group title	Dose Escalation Level 4
Reporting group description:	
520 mg/m2 BID = 1040 mg/m2/day	
Reporting group title	Dose Escalation Level 5
Reporting group description:	
700 mg/m2 BID = 1400 mg/m2/day	
Reporting group title	Dose Escalation Level 6
Reporting group description:	
900 mg/m2 BID = 1800 mg/m2/day	
Reporting group title	Dose Escalation Level 7
Reporting group description:	
1200 mg/m2 BID = 2400 mg/m2/day	
Reporting group title	Dose Expansion Cohort 1
Reporting group description:	
Subjects with ATRT	
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	
Reporting group title	Dose Expansion Cohort 3
Reporting group description:	
Subjects with INI1-negative tumors	
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	

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)	3	3	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 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	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%)	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 / 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 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
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)	0	1	2
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%)	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	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 / 2
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 / 1	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 / 1	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 / 1
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 Level 7	Dose Expansion Cohort 1	Dose Expansion 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)	1	6	8
number of deaths resulting from adverse events	0	0	1
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 / 0
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 / 1	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 / 0
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%)	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
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%)	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
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 / 1
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 / 4	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	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
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 / 1	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 / 1
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 / 1
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 / 1	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 / 1	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)	2	2	
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 / 1	
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	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	
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 / 1	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	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	
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	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			

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	
Gastrointestinal disorders			
Abdominal 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	
Constipation			
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	
Intestinal obstruction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 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	
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
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	
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)	1	0	0
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	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	2
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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	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	1	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
Psychiatric disorders			
Irritability			
subjects affected / exposed	3 / 8 (37.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Investigations			

Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bromide 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
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
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)	1	0	1
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
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
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	1	2	3
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	0	2	3
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	1	2	3
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	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%)	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	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	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 (all)	0	0	0
Pain in extremity			
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	1	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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypermagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
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)	1	1	0
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
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	3	2
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Asthenia			
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	3	3
Nasal congestion			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
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	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
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	3 / 6 (50.00%)
occurrences (all)	1	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Lymphocyte count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Blood bromide 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)	2	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
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	2	2
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	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	1
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
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	2	3	2
Nausea			

subjects affected / exposed	1 / 7 (14.29%)	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	1	3	2
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	4 / 6 (66.67%)	2 / 6 (33.33%)
occurrences (all)	2	4	2
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Stomatitis			
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	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	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 (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
Infections and infestations			

Otitis media			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urinary tract infection			
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	1	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%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	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

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	2	2
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	3 / 20 (15.00%)
occurrences (all)	1	1	3
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	4	5
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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 7 (28.57%)	6 / 19 (31.58%)	4 / 20 (20.00%)
occurrences (all)	2	6	4
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	1	1
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2

Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	1	2	1
Lymphocyte count decreased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	3 / 20 (15.00%)
occurrences (all)	1	2	3
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	3 / 20 (15.00%)
occurrences (all)	0	1	3
Blood bromide increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	0	2	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
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 7 (14.29%)	4 / 19 (21.05%)	1 / 20 (5.00%)
occurrences (all)	1	4	1
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 19 (21.05%)	8 / 20 (40.00%)
occurrences (all)	2	4	8
Lymphopenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 7 (85.71%)	11 / 19 (57.89%)	9 / 20 (45.00%)
occurrences (all)	6	11	9
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	7	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
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%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Infections and infestations			
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	1 / 20 (5.00%)
occurrences (all)	1	2	1
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
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	3	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	1	1
Hypermagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	2 / 20 (10.00%)
occurrences (all)	0	2	2

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	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 18 (11.11%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	5 / 18 (27.78%)	2 / 6 (33.33%)	
occurrences (all)	5	2	
Pyrexia			
subjects affected / exposed	7 / 18 (38.89%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Oedema peripheral			
subjects affected / exposed	5 / 18 (27.78%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Asthenia			
subjects affected / exposed	1 / 18 (5.56%)	3 / 6 (50.00%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 18 (33.33%)	3 / 6 (50.00%)	
occurrences (all)	6	3	
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	3	
Hypoxia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 18 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
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	
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	2	
Blood bromide increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 18 (38.89%)	3 / 6 (50.00%)	
occurrences (all)	7	3	
Dizziness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
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)	5	0	
Lymphopenia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	3	
Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	11 / 18 (61.11%)	5 / 6 (83.33%)	
occurrences (all)	11	5	
Nausea			
subjects affected / exposed	11 / 18 (61.11%)	3 / 6 (50.00%)	
occurrences (all)	11	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)	7	2	
Abdominal pain			
subjects affected / exposed	3 / 18 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Stomatitis			
subjects affected / exposed	3 / 18 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
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)	2	0	
Alopecia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
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	
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)	1	1	
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	
occurrences (all)	1	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	1	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	
occurrences (all)	2	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	

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: - 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: - Added selected tumors with rhabdoid features that responses were seen in Phase 1 (SMARCA4 loss in MRTO 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: - 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: - 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: - Removal of synovial and other INI1-negative/SMARCA4 negative tumors
11 May 2016	Amendment v3.0 – submitted to all sites. Key changes: - 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: - 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/m2 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/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

03 August 2017	Amendment v5.1 – Country-specific for Germany Key changes: - 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	Amendment v5.4 – Country-specific for France Key changes: - 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	Amendment v5.5 – Country-specific for France Key changes: - Option to change from suspension to tablets
28 September 2018	Amendment v6.0 – submitted to all sites Key changes: - 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/m2 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	Amendment v8.0 – submitted to all sites. Key changes: - 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 internal from 90% to 95% to be estimated in the case of sufficient number of deaths to trigger survival endpoint assessments by Brookneyer-Crowley.
03 April 2020	Amendment v8.2 – Country-specific for United Kingdom - All changed from v8.0 incorporated
03 April 2020	Amendment v8.3 – Country-specific for Germany - All changed from v8.0 incorporated
01 July 2020	Amendment v8.4 – Country-specific for Germany Key changes: - 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

06 April 2018	On 06 April 2018, an event of T-LBL was observed in a pediatric subject on study EZH-102. 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. 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. 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. To date, no adult T-LBL/T-ALL cases have occurred.	28 September 2018

Notes:

Limitations and caveats

None reported