Clinical trial results:
A Phase 1/2 Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors

Summary

EudraCT number	2022-003736-77
Trial protocol	Outside EU/EEA
Global end of trial date	30 September 2022

Results information

Result version number	v1 (current)
This version publication date	15 April 2023
First version publication date	15 April 2023

Trial information

Trial identification

Sponsor protocol code	E7080-A001-216

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03245151
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	200 Metro Blvd, Nutley, New Jersey, United States, 07110
Public contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_medinfo@eisai.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001119-PIP03-19
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1 of this study, utilizing a rolling 6 design, was conducted to determine a maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D), and to describe the toxicities of lenvatinib administered in combination with everolimus once daily to pediatric subjects with recurrent/refractory solid tumors. Phase 2, utilizing Simon's optimal 2-stage design, was conducted to estimate the antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with selected recurrent/refractory solid tumors including Ewing sarcoma (EWS), rhabdomyosarcoma (RMS), and high grade glioma (HGG) using objective response rate (ORR) at Week 16 as the endpoint.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 62
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	64
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	31
Adolescents (12-17 years)	21
Adults (18-64 years)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 24 investigative sites in the United States and Canada from 16 November 2017 to 30 September 2022.

Pre-assignment

Screening details:

A total of 86 subjects were screened, out of which 64 were enrolled and 9 subjects completed the study.

Period 1

Period 1 title	Overall (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	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2

Arm description:

Subjects with recurrent or refractory solid tumors received lenvatinib 8 milligram per square meter (mg/m^2), capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of disease progression (PD), clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory solid tumors received lenvatinib 8 mg/m^2, capsules, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory solid tumors received everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Arm title	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2

Arm description:

Subjects with recurrent or refractory solid tumors received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory solid tumors received everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory solid tumors received lenvatinib 11 mg/m^2, capsules, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Arm title	Phase 2: Cohort 1, Ewing sarcoma

Arm description:

Subjects with recurrent or refractory ewing sarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory ewing sarcoma received everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory ewing sarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Arm title	Phase 2: Cohort 2, Rhabdomyosarcoma

Arm description:

Subjects with recurrent or refractory rhabdomyosarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory rhabdomyosarcoma received everolimus 3 mg/m^2, tablets, orally,

once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory rhabdomyosarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Arm title	Phase 2: Cohort 3, High Grade Glioma

Arm description:

Subjects with recurrent or refractory HGG received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory HCG received everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects with recurrent or refractory HCG received lenvatinib 11 mg/m^2, capsules, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Number of subjects in period 1	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2	Phase 2: Cohort 1, Ewing sarcoma
Started	5	18	10
Completed	0	3	1
Not completed	5	15	9
Sponsor's decision	-	1	-
Consent withdrawn by subject	2	-	-
Death	3	14	9

Number of subjects in period 1	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma
Started	20	11
Completed	2	3
Not completed	18	8
Sponsor's decision	-	-

Consent withdrawn by subject	2	1
Death	16	7

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2
Reporting group description:	
Subjects with recurrent or refractory solid tumors received lenvatinib 8 milligram per square meter (mg/m^2), capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of disease progression (PD), clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.	
Reporting group title	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2
Reporting group description:	
Subjects with recurrent or refractory solid tumors received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.	
Reporting group title	Phase 2: Cohort 1, Ewing sarcoma
Reporting group description:	
Subjects with recurrent or refractory ewing sarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.	
Reporting group title	Phase 2: Cohort 2, Rhabdomyosarcoma
Reporting group description:	
Subjects with recurrent or refractory rhabdomyosarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.	
Reporting group title	Phase 2: Cohort 3, High Grade Glioma
Reporting group description:	
Subjects with recurrent or refractory HGG received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.	

Reporting group values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2	Phase 2: Cohort 1, Ewing sarcoma
Number of subjects	5	18	10
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	16	3
Adolescents (12-17 years)	4	1	3
Adults (18-64 years)	1	1	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender Categorical Units: Subjects			
Female	2	10	3
Male	3	8	7

Ethnicity Units: Subjects			
Hispanic or Latino	1	7	2
Not Hispanic or Latino	4	11	8
Race Units: Subjects			
White	3	11	9
Black or African American	1	1	0
Asian	0	1	1
Not Specified	1	4	0
American Indian or Alaskan Native	0	1	0

Reporting group values	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	Total
Number of subjects	20	11	64
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	9	3	31
Adolescents (12-17 years)	6	7	21
Adults (18-64 years)	5	1	12
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender Categorical Units: Subjects			
Female	8	8	31
Male	12	3	33
Ethnicity Units: Subjects			
Hispanic or Latino	2	0	12
Not Hispanic or Latino	18	11	52
Race Units: Subjects			
White	16	6	45
Black or African American	1	3	6
Asian	0	0	2
Not Specified	3	2	10
American Indian or Alaskan Native	0	0	1

End points

End points reporting groups

Reporting group title	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2

Reporting group description:

Subjects with recurrent or refractory solid tumors received lenvatinib 8 milligram per square meter (mg/m^2), capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of disease progression (PD), clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Reporting group title	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2

Reporting group description:

Subjects with recurrent or refractory solid tumors received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Reporting group title	Phase 2: Cohort 1, Ewing sarcoma

Reporting group description:

Subjects with recurrent or refractory ewing sarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Reporting group title	Phase 2: Cohort 2, Rhabdomyosarcoma

Reporting group description:

Subjects with recurrent or refractory rhabdomyosarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Reporting group title	Phase 2: Cohort 3, High Grade Glioma

Reporting group description:

Subjects with recurrent or refractory HGG received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Subject analysis set title	Phase 1: Lenvatinib + Everolimus (All Subjects)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with recurrent or refractory solid tumors received lenvatinib 8 or 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Primary: Phase 1: Maximum Tolerated Dose (MTD) of Lenvatinib in Combination with Everolimus

End point title	Phase 1: Maximum Tolerated Dose (MTD) of Lenvatinib in Combination with Everolimus[1]

End point description:

MTD was defined as the highest dose level at which no more than 1/6 subjects experienced a dose limiting toxicity (DLTs), with the next higher dose having at least 0 of 3 or 1 of 6 subjects experiencing DLTs. DLT was graded according to common terminology criteria for adverse events (CTCAE) v4.03. Safety analysis set (SAS) included all subjects who received at least one dose of study drug (Lenvatinib or Everolimus).

End point type	Primary

End point timeframe:

Cycle 1 (28 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was planned for this primary endpoint.

End point values	Phase 1: Lenvatinib + Everolimus (All Subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: milligram per square meter (mg/m^2)				
number (not applicable)	11			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of Subjects with any Treatment-emergent Adverse Event (TEAE)

End point title	Phase 1: Number of Subjects with any Treatment-emergent Adverse Event (TEAE)[2][3]

End point description:

A TEAE was defined as an adverse event that emerged during treatment, having been absent at pretreatment or reemerged during treatment, having been present at pretreatment but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the adverse event is continuous. An adverse event was defined as any untoward medical occurrence in a subject administered an investigational product. SAS included all subjects who received at least one dose of study drug (Lenvatinib or Everolimus).

End point type	Primary

End point timeframe:

From date of first dose up to 28 days after the last dose of study treatment (Up to 17.5 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was planned for this primary endpoint.

[3] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	18		
Units: subjects	5	18		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of Subjects with any Treatment-emergent Serious Adverse Event (TESAE)

End point title	Phase 1: Number of Subjects with any Treatment-emergent Serious Adverse Event (TESAE)[4][5]

End point description:

A TESAE was any untoward medical occurrence that at any dose: resulted in death; life threatening condition; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect or was medically important due to other reasons than the above mentioned criteria. An adverse event was defined as any untoward medical occurrence in a subject administered an investigational product. SAS included all subjects who received at least one dose of study drug (Lenvatinib or Everolimus).

End point type	Primary

End point timeframe:

From date of first dose up to 28 days after the last dose of study treatment (Up to 17.5 months)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was planned for this primary endpoint.

[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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	18		
Units: subjects	2	12		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Recommended Phase 2 Dose (RP2D) of Lenvatinib in Combination with Everolimus

End point title	Phase 1: Recommended Phase 2 Dose (RP2D) of Lenvatinib in Combination with Everolimus[6]

End point description:

The RP2D of lenvatinib in combination with everolimus was determined by Dose Escalation Committee (DEC) based on safety, pharmacokinetic and clinical data. DLT was graded according to CTCAE v4.03. SAS included all subjects who received at least one dose of study drug (Lenvatinib or Everolimus).

End point type	Primary

End point timeframe:

Cycle 1 (28 days)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was planned for this primary endpoint.

End point values	Phase 1: Lenvatinib + Everolimus (All Subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: mg/m^2				
number (not applicable)	11			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Objective Response Rate (ORR) at Week 16

End point title	Phase 2: Objective Response Rate (ORR) at Week 16[7][8]

End point description:

ORR at Week 16 was defined as the percentage of subjects whose best overall response (BOR) was confirmed complete response (CR) or partial response (PR) at Week 16 based on investigator assessment according to response evaluation criteria in solid tumors (RECIST) version 1.1 for non-HGG cohorts and response assessment in neuro-oncology (RANO) for HGG cohort. Evaluable analysis set included all evaluable subjects who have measurable disease present at baseline, and at least one postbaseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease.

End point type	Primary

End point timeframe:

Week 16

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was planned for this primary endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 2: Cohort 1, Ewing sarcoma	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	20	10	
Units: percentage of subjects				
number (confidence interval 95%)	0.0 (0.0 to 30.8)	10.0 (1.2 to 31.7)	0 (0.0 to 30.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Objective Response Rate (ORR)

End point title	Phase 2: Objective Response Rate (ORR)[9]

End point description:

ORR was defined as the percentage of subjects whose BOR was confirmed CR or PR based on investigator assessment according to RECIST version 1.1 for non-HGG cohorts and RANO for HGG cohort. Evaluable analysis set included all evaluable subjects who have measurable disease present at baseline, and at least one postbaseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease.

End point type	Secondary

End point timeframe:

From first dose date until PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination (up to 5.6 months)

Notes:

[9] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 2: Cohort 1, Ewing sarcoma	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	20	10	
Units: percentage of subjects				
number (confidence interval 95%)	0.0 (0.0 to 30.8)	10.0 (1.2 to 31.7)	0.0 (0.0 to 30.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Objective Response Rate (ORR)

End point title	Phase 1: Objective Response Rate (ORR)[10]

End point description:

ORR was defined as the percentage of subjects whose BOR was confirmed CR or PR based on investigator assessment according to RECIST version 1.1 for non-HGG cohorts and RANO for HGG cohort. SAS included all subjects who received at least 1 dose of study drug (lenvatinib or everolimus). Here, N 'number of subjects analyzed' signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose date until PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination (up to 17 months)

Notes:

[10] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	15		
Units: percentage of subjects				
number (confidence interval 95%)	0.0 (0.0 to	0.0 (0.0 to		

70.8)	21.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Disease Control Rate (DCR)

End point title	Phase 2: Disease Control Rate (DCR)[11]

End point description:

DCR: percentage of subjects with confirmed CR, PR, or SD (SD duration >=7 weeks since first dose of study treatment) divided by number of subjects in analysis set. DCR was assessed by investigator based on RECIST v1.1 for non-HGG cohorts or RANO for HGG cohort. Evaluable analysis set: evaluable subjects who have measurable disease present at baseline, and at least one postbaseline efficacy assessment, unless they have discontinued prior to first efficacy assessment due to PD.

End point type	Secondary

End point timeframe:

From first dose date until PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination (up to 5.6 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 2: Cohort 1, Ewing sarcoma	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	20	10	
Units: percentage of subjects				
number (confidence interval 95%)	40.0 (12.2 to 73.8)	40.0 (19.1 to 63.9)	30.0 (6.7 to 65.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Disease Control Rate (DCR)

End point title	Phase 1: Disease Control Rate (DCR)[12]

End point description:

DCR: percentage of subjects with a confirmed CR, PR, or stable disease (SD) (SD duration >=7 weeks since the first dose of study treatment) divided by number of subjects in analysis set. DCR was assessed by an investigator based on RECIST v1.1 for non-HGG subjects or RANO for HGG subjects. SAS included all subjects who received at least 1 dose of study drug (lenvatinib or everolimus).

End point type	Secondary

End point timeframe:

From first dose date until PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination (up to 17 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	18		
Units: Percentage of subjects				
number (confidence interval 95%)	20.0 (0.5 to 71.6)	50.0 (26.0 to 74.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Clinical Benefit Rate (CBR)

End point title	Phase 1: Clinical Benefit Rate (CBR)[13]

End point description:

CBR: percentage of subjects with a confirmed CR, PR, or SD (SD duration >=23 weeks since the first dose of study treatment) divided by number of subjects in analysis set. CBR was assessed by an investigator based on RECIST v1.1 for non-HGG subjects or RANO for HGG subjects. SAS included all subjects who received at least 1 dose of study drug (lenvatinib or everolimus).

End point type	Secondary

End point timeframe:

From first dose date until PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination (up to 17 months)

Notes:

[13] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	18		
Units: percentage of subjects				
number (confidence interval 95%)	20.0 (0.5 to 71.6)	22.2 (6.4 to 47.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Duration of Response (DOR)

End point title	Phase 1: Duration of Response (DOR)[14]

End point description:

DOR: time (in months) from the date of first observation of confirmed response (PR or CR) to the date of the first observation of progression based on the investigator's assessment utilizing RECIST 1.1 for non-HGG cohorts and RANO for HGG cohorts, or date of death, whatever the cause. SAS included all subjects who received at least 1 dose of study drug (lenvatinib or everolimus).

End point type	Secondary

End point timeframe:

From date of the first observation of CR or PR until the date of first observation of progression or date of death up to 17 months

Notes:

[14] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[15] - No subject was analyzed for this arm.

[16] - No subject was analyzed for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Clinical Benefit Rate (CBR)

End point title	Phase 2: Clinical Benefit Rate (CBR)[17]

End point description:

CBR: percentage of subjects with a confirmed CR, PR, or SD (SD duration >=23 weeks since the first dose of study treatment) divided by number of subjects in analysis set. CBR was assessed by an investigator based on RECIST v1.1 for non-HGG cohorts or RANO for HGG cohort. Evaluable analysis set included all evaluable subjects who have measurable disease present at baseline, and at least one postbaseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to PD.

End point type	Secondary

End point timeframe:

From first dose date until PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination (up to 5.6 months)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 2: Cohort 1, Ewing sarcoma	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	20	10	
Units: percentage of subjects				
number (confidence interval 95%)	20.0 (2.5 to 55.6)	10.0 (1.2 to 31.7)	0.0 (0.0 to 30.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration of Lenvatinib AUC(0-t Hours)

End point title	Phase 1: Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration of Lenvatinib AUC(0-t Hours)[18]

End point description:

Pharmacokinetic analysis set included subjects who had at least one measurable postdose plasma concentration with an adequately documented drug administration history. Here, n 'number of subjects analyzed' signifies subjects who were evaluable for this endpoint at given categories. Pharmacokinetic data was planned to be analyzed for Phase 1 only.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1 and 15: 0-8 hours post-dose (Cycle length=28 days)

Notes:

[18] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	18		
Units: nanogram*hour per milliliter (ng*hr/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=5, 18)	2338.0 (± 1633.41)	3281.1 (± 1064.72)		
Cycle 1 Day 15 (n=5, 17)	1328.0 (± 520.69)	2139.8 (± 1156.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

End point title	Phase 2: Duration of Response (DOR)[19]

End point description:

DOR: time (in months) from the date of first observation of confirmed response (PR or CR) to the date of the first observation of progression based on the investigator's assessment utilizing RECIST 1.1 for non-HGG cohorts and RANO for HGG cohort, or date of death, whatever the cause. Evaluable analysis set included all evaluable subjects who have measurable disease present at baseline, and at least one postbaseline efficacy assessment, unless they have discontinued prior to first efficacy assessment due to progressive disease. Here 99999 refers to 95% CI was not estimated.

End point type	Secondary

End point timeframe:

From date of the first observation of CR or PR until the date of first observation of progression or date of death up to 5.6 months

Notes:

[19] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 2: Cohort 1, Ewing sarcoma	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[20]	2	0[21]	
Units: months				
median (confidence interval 95%)	(to)	2.4 (2.1 to 99999)	(to)	

Notes:

[20] - No subject was analyzed for this arm.

[21] - No subject was analyzed for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Maximum Plasma Concentration of Lenvatinib (Cmax)

End point title	Phase 1: Maximum Plasma Concentration of Lenvatinib

End point description:

Pharmacokinetic analysis set included subjects who had at least one measurable postdose plasma concentration with an adequately documented drug administration history. Here, n 'number of subjects analyzed' signifies subjects who were evaluable for this endpoint at given categories. Pharmacokinetic data was planned to be analyzed for Phase 1 only.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1 and 15: 0-8 hours post-dose (Cycle length=28 days)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	18		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=5, 18)	240.20 (± 130.892)	404.13 (± 121.473)		
Cycle 1 Day 15 (n=5, 17)	314.20 (± 149.527)	447.62 (± 272.790)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Time to Reach Maximum Plasma Concentration (Cmax) of Lenvatinib (Tmax)

End point title	Phase 1: Time to Reach Maximum Plasma Concentration (Cmax) of Lenvatinib (Tmax)[23]

End point description:

Pharmacokinetic analysis set included subjects who had at least one measurable postdose plasma concentration with an adequately documented drug administration history. Here, n 'number of subjects analyzed' signifies subjects who were evaluable for this endpoint at given categories. Pharmacokinetic data was planned to be analyzed for Phase 1 only.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1 and 15: 0-8 hours post-dose (Cycle length=28 days)

Notes:

[23] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	18		
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1 (n=5, 18)	3.000 (2.000 to 4.000)	2.890 (1.000 to 7.78)		
Cycle 1 Day 15 (n=5, 17)	3.950 (2.000 to 8.05)	2.950 (0 to 8.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Subjects with any Treatment-emergent Adverse Event (TEAE)

End point title	Phase 2: Number of Subjects with any Treatment-emergent Adverse Event (TEAE)[24]

End point description:

A TEAE was defined as an adverse event that emerged during treatment, having been absent at pretreatment or reemerged during treatment, having been present at pretreatment but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the adverse event is continuous. An adverse event was defined as any untoward medical occurrence in a subject administered an investigational product. SAS included all subjects who received at least one dose of study drug (Lenvatinib or Everolimus).

End point type	Secondary

End point timeframe:

From date of first dose up to 28 days after the last dose of study treatment (Up to 6.5 months)

Notes:

[24] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 2: Cohort 1, Ewing sarcoma	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	20	11	
Units: subjects	10	19	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Subjects with any Treatment-emergent Serious Adverse Event (TESAE)

End point title	Phase 2: Number of Subjects with any Treatment-emergent Serious Adverse Event (TESAE)[25]

End point description:

A TESAE was any untoward medical occurrence that at any dose: resulted in death; life threatening condition; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect or was medically important due to other reasons than the above mentioned criteria. An adverse event was defined as any untoward medical occurrence in a subject administered an investigational product. SAS included all subjects who received at least one dose of study drug (Lenvatinib or Everolimus).

End point type	Secondary

End point timeframe:

From date of first dose up to 28 days after the last dose of study treatment (Up to 6.5 months)

Notes:

[25] - 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: This endpoint was planned to be analysed for specified arms only.

End point values	Phase 2: Cohort 1, Ewing sarcoma	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 3, High Grade Glioma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	20	11	
Units: subjects	6	8	8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose up to 28 days after the last dose of study treatment (Phase 1: Up to 17.5 months; Phase 2: Up to 6.5 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2

Reporting group description:

Subjects with recurrent or refractory solid tumors received lenvatinib 8 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Reporting group title	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2

Reporting group description:

Subjects with recurrent or refractory solid tumors received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily in cycle 1 (each cycle was 28 days) until the occurrence of PD, clinical benefit, development of unacceptable toxicity leading to withdrawal from the study, study termination or for a maximum of 18 cycles (each cycle was 28 days) whichever occurred first.

Reporting group title	Phase 2: Cohort 3, High Grade Glioma (HGG)

Reporting group description:

Subjects with recurrent or refractory HCG received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Reporting group title	Phase 2: Cohort 2, Rhabdomyosarcoma

Reporting group description:

Subjects with recurrent or refractory rhabdomyosarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Reporting group title	Phase 2: Cohort 1, Ewing sarcoma

Reporting group description:

Subjects with recurrent or refractory ewing sarcoma received lenvatinib 11 mg/m^2, capsules, orally, once daily in combination with everolimus 3 mg/m^2, tablets, orally, once daily for up to 7 cycles (each cycle was 28 days) unless subject discontinued early from the study.

Serious adverse events	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2	Phase 2: Cohort 3, High Grade Glioma (HGG)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	12 / 18 (66.67%)	8 / 11 (72.73%)
number of deaths (all causes)	4	14	8
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Malignant pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Cancer pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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 / 5 (0.00%)	3 / 18 (16.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	3 / 18 (16.67%)	2 / 11 (18.18%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nystagmus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Dysarthria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Hydrocephalus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Encephalopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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			
Eyelid oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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 cavity fistula			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (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
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (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
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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 chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
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 aspiration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper respiratory tract infections			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 1, Ewing sarcoma	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)	6 / 10 (60.00%)	
number of deaths (all causes)	17	9	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (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 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (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			
Pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	3 / 10 (30.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 20 (5.00%)	2 / 10 (20.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Alanine aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (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			
Tendon rupture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nystagmus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Depressed level of consciousness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (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 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral cavity fistula			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia aspiration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infections			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
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: 0 %

Non-serious adverse events	Phase 1: Lenvatinib 8 mg/m^2 + Everolimus 3 mg/m^2	Phase 1: Lenvatinib 11 mg/m^2 + Everolimus 3 mg/m^2	Phase 2: Cohort 3, High Grade Glioma (HGG)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	18 / 18 (100.00%)	11 / 11 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrous cortical defect			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tumour haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Cancer pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Malignant pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 5 (80.00%)	13 / 18 (72.22%)	4 / 11 (36.36%)
occurrences (all)	14	19	5
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	5 / 18 (27.78%)	0 / 11 (0.00%)
occurrences (all)	1	7	0
Localised oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	3 / 5 (60.00%)	6 / 18 (33.33%)	3 / 11 (27.27%)
occurrences (all)	4	9	5
Pain			
subjects affected / exposed	3 / 5 (60.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	7	2	1
Oedema peripheral			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Gait disturbances			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	3 / 18 (16.67%)	1 / 11 (9.09%)
occurrences (all)	0	7	1
Malaise			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Dysphonia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Cough			

subjects affected / exposed	1 / 5 (20.00%)	4 / 18 (22.22%)	1 / 11 (9.09%)
occurrences (all)	1	7	1
Atelectasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tachypnoea			
subjects affected / exposed	0 / 5 (0.00%)	3 / 18 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Productive cough			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)	4 / 18 (22.22%)	1 / 11 (9.09%)
occurrences (all)	1	4	1
Nasal congestion			
subjects affected / exposed	2 / 5 (40.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	2	3	0
Hypoxia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Hiccups			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Respiratory distress			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pulmonary oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 5 (40.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	3	1	1
Anxiety			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	2	3	1
Irritability			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Restlessness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	2 / 5 (40.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	3	4	1
Product issues			
Device dislocation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	5 / 18 (27.78%)	3 / 11 (27.27%)
occurrences (all)	0	10	4
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Blood fibrinogen decreased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Haemoglobin increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 18 (16.67%)	3 / 11 (27.27%)
occurrences (all)	0	4	5
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 5 (40.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	2	2	0
Ejection fraction decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	5 / 18 (27.78%)	4 / 11 (36.36%)
occurrences (all)	0	13	5
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	1	1	3
Blood cholesterol increased			
subjects affected / exposed	1 / 5 (20.00%)	6 / 18 (33.33%)	4 / 11 (36.36%)
occurrences (all)	1	23	12
Blood creatinine increased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	2	3
Weight decreased			
subjects affected / exposed	2 / 5 (40.00%)	6 / 18 (33.33%)	0 / 11 (0.00%)
occurrences (all)	3	12	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Platelet count increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	3 / 5 (60.00%)	4 / 18 (22.22%)	2 / 11 (18.18%)
occurrences (all)	6	12	9
Lymphocyte count decreased			
subjects affected / exposed	3 / 5 (60.00%)	6 / 18 (33.33%)	2 / 11 (18.18%)
occurrences (all)	14	13	10
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
White blood cell count decreased			
subjects affected / exposed	2 / 5 (40.00%)	6 / 18 (33.33%)	2 / 11 (18.18%)
occurrences (all)	7	16	8
Platelet count decreased			
subjects affected / exposed	2 / 5 (40.00%)	7 / 18 (38.89%)	3 / 11 (27.27%)
occurrences (all)	6	22	4
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	3	1
Fall			

subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	2
Stoma site pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tendon rupture			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Wrist fracture			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Wound complication			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Wound dehiscence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Allergic transfusion reaction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	2 / 5 (40.00%)	4 / 18 (22.22%)	0 / 11 (0.00%)
occurrences (all)	6	5	0

Bradycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Dysarthria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	3 / 5 (60.00%)	8 / 18 (44.44%)	5 / 11 (45.45%)
occurrences (all)	14	10	7
Hydrocephalus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Hypersomnia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Lethargy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Tremor			

subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Intracranial haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)	6 / 18 (33.33%)	1 / 11 (9.09%)
occurrences (all)	6	16	5
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Miosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 5 (20.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	3	1	0
Abdominal pain			
subjects affected / exposed	3 / 5 (60.00%)	9 / 18 (50.00%)	4 / 11 (36.36%)
occurrences (all)	4	16	5
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Anal incontinence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Gingival pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Cheilitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	2 / 5 (40.00%)	3 / 18 (16.67%)	3 / 11 (27.27%)
occurrences (all)	4	4	3
Diarrhoea			
subjects affected / exposed	3 / 5 (60.00%)	10 / 18 (55.56%)	7 / 11 (63.64%)
occurrences (all)	10	23	9
Dry mouth			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Aphthous ulcer			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Nausea			
subjects affected / exposed	4 / 5 (80.00%)	5 / 18 (27.78%)	4 / 11 (36.36%)
occurrences (all)	9	8	5
Mouth haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	4 / 5 (80.00%)	5 / 18 (27.78%)	2 / 11 (18.18%)
occurrences (all)	10	8	3
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pancreatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 5 (60.00%)	11 / 18 (61.11%)	7 / 11 (63.64%)
occurrences (all)	10	20	10
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Hepatobiliary disorders			
Steatohepatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	4
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 5 (20.00%)	1 / 18 (5.56%)	2 / 11 (18.18%)
occurrences (all)	1	1	5
Pruritus			

subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	6	0
Dermatitis contact			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 5 (20.00%)	4 / 18 (22.22%)	1 / 11 (9.09%)
occurrences (all)	1	6	1
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Scab			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Skin atrophy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Erythemas			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Petechiae			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 5 (20.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Pollakiuria			
subjects affected / exposed	2 / 5 (40.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	3 / 11 (27.27%)
occurrences (all)	1	2	3
Proteinuria			
subjects affected / exposed	1 / 5 (20.00%)	8 / 18 (44.44%)	4 / 11 (36.36%)
occurrences (all)	4	37	4
Micturition urgency			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Renal tubular dysfunction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Glycosuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Urinary retention			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	2	3	0
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Hypothyroidism			
subjects affected / exposed	2 / 5 (40.00%)	10 / 18 (55.56%)	6 / 11 (54.55%)
occurrences (all)	3	13	7
Hyperparathyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	4 / 18 (22.22%)	2 / 11 (18.18%)
occurrences (all)	1	9	3
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	3 / 5 (60.00%)	2 / 18 (11.11%)	2 / 11 (18.18%)
occurrences (all)	4	5	2
Muscular weakness			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Back pain			
subjects affected / exposed	4 / 5 (80.00%)	1 / 18 (5.56%)	2 / 11 (18.18%)
occurrences (all)	4	1	2
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	3 / 11 (27.27%)
occurrences (all)	3	3	5
Joint range of motion decreased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	1	3	0
Spinal pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pain in jaw			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Periostitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Myositis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Muscle spasms			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Sinusitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infections			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0

Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Device related infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	2 / 5 (40.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	3 / 18 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 5 (80.00%)	4 / 18 (22.22%)	2 / 11 (18.18%)
occurrences (all)	7	5	2
Hypermagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Hyperkalaemia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Hypercholesterolaemia			

subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Hypercalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 18 (22.22%)	3 / 11 (27.27%)
occurrences (all)	0	5	7
Dehydration			
subjects affected / exposed	2 / 5 (40.00%)	2 / 18 (11.11%)	0 / 11 (0.00%)
occurrences (all)	2	5	0
Hypertriglyceridaemia			
subjects affected / exposed	2 / 5 (40.00%)	11 / 18 (61.11%)	6 / 11 (54.55%)
occurrences (all)	3	51	22
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	1 / 11 (9.09%)
occurrences (all)	1	2	2
Hypocholesterolaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 18 (22.22%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 18 (22.22%)	0 / 11 (0.00%)
occurrences (all)	0	9	0
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)	6 / 18 (33.33%)	1 / 11 (9.09%)
occurrences (all)	1	7	1
Hypophosphataemia			
subjects affected / exposed	1 / 5 (20.00%)	3 / 18 (16.67%)	1 / 11 (9.09%)
occurrences (all)	1	6	1
Hypoglycaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Non-serious adverse events	Phase 2: Cohort 2, Rhabdomyosarcoma	Phase 2: Cohort 1, Ewing sarcoma	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)	10 / 10 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrous cortical defect			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Tumour haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Tumour pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Cancer pain			
subjects affected / exposed	1 / 20 (5.00%)	2 / 10 (20.00%)	
occurrences (all)	3	3	
Malignant pleural effusion			
subjects affected / exposed	0 / 20 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 20 (50.00%)	3 / 10 (30.00%)	
occurrences (all)	18	4	
Hot flush			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Hypotension			

subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 20 (15.00%)	4 / 10 (40.00%)	
occurrences (all)	4	8	
Localised oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	11 / 20 (55.00%)	6 / 10 (60.00%)	
occurrences (all)	16	7	
Pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
Oedema peripheral			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Gait disturbances			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Face oedema			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Non-cardiac chest pain			

subjects affected / exposed	5 / 20 (25.00%)	1 / 10 (10.00%)	
occurrences (all)	8	1	
Malaise			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	6 / 20 (30.00%)	1 / 10 (10.00%)	
occurrences (all)	9	1	
Dyspnoea			
subjects affected / exposed	4 / 20 (20.00%)	2 / 10 (20.00%)	
occurrences (all)	5	2	
Dysphonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	4 / 20 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	5	1	
Atelectasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Tachypnoea			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	4	1	
Productive cough			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Rhinitis allergic			

subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pneumothorax			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Pleural effusion			
subjects affected / exposed	1 / 20 (5.00%)	2 / 10 (20.00%)	
occurrences (all)	1	5	
Oropharyngeal pain			
subjects affected / exposed	7 / 20 (35.00%)	2 / 10 (20.00%)	
occurrences (all)	12	3	
Nasal congestion			
subjects affected / exposed	5 / 20 (25.00%)	1 / 10 (10.00%)	
occurrences (all)	5	1	
Hypoxia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 10 (20.00%)	
occurrences (all)	1	3	
Hiccups			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Respiratory distress			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Pulmonary oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Anxiety			
subjects affected / exposed	4 / 20 (20.00%)	2 / 10 (20.00%)	
occurrences (all)	4	2	

Irritability			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Restlessness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Agitation			
subjects affected / exposed	2 / 20 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	2	3	
Insomnia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 20 (35.00%)	3 / 10 (30.00%)	
occurrences (all)	7	7	
Amylase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Blood fibrinogen decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	3	2	
International normalised ratio increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

Haemoglobin increased				
subjects affected / exposed	3 / 20 (15.00%)	1 / 10 (10.00%)		
occurrences (all)	9	1		
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)		
occurrences (all)	0	0		
Ejection fraction decreased				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Blood lactate dehydrogenase increased				
subjects affected / exposed	2 / 20 (10.00%)	2 / 10 (20.00%)		
occurrences (all)	2	3		
Aspartate aminotransferase increased				
subjects affected / exposed	8 / 20 (40.00%)	4 / 10 (40.00%)		
occurrences (all)	13	6		
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)		
occurrences (all)	1	1		
Blood cholesterol increased				
subjects affected / exposed	11 / 20 (55.00%)	2 / 10 (20.00%)		
occurrences (all)	14	2		
Blood creatinine increased				
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)		
occurrences (all)	4	2		
Weight increased				
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)		
occurrences (all)	0	0		
Weight decreased				
subjects affected / exposed	6 / 20 (30.00%)	1 / 10 (10.00%)		
occurrences (all)	10	2		
SARS-CoV-2 test positive				
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)		
occurrences (all)	0	0		
Platelet count increased				

subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	7 / 20 (35.00%)	3 / 10 (30.00%)	
occurrences (all)	14	7	
Lymphocyte count decreased			
subjects affected / exposed	11 / 20 (55.00%)	8 / 10 (80.00%)	
occurrences (all)	32	27	
Lipase increased			
subjects affected / exposed	4 / 20 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	6	0	
White blood cell count decreased			
subjects affected / exposed	8 / 20 (40.00%)	6 / 10 (60.00%)	
occurrences (all)	24	17	
Platelet count decreased			
subjects affected / exposed	10 / 20 (50.00%)	5 / 10 (50.00%)	
occurrences (all)	21	9	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Stoma site pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Tendon rupture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Wrist fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Procedural pain			

subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Wound complication			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Wound dehiscence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Allergic transfusion reaction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Sinus tachycardia			
subjects affected / exposed	3 / 20 (15.00%)	1 / 10 (10.00%)	
occurrences (all)	5	2	
Bradycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Dysarthria			

subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Headache			
subjects affected / exposed	5 / 20 (25.00%)	1 / 10 (10.00%)	
occurrences (all)	5	1	
Hydrocephalus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Hypersomnia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Lethargy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Seizure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Intracranial haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

Neutropenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Anaemia			
subjects affected / exposed	7 / 20 (35.00%)	5 / 10 (50.00%)	
occurrences (all)	10	17	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Miosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Eye pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	7 / 20 (35.00%)	1 / 10 (10.00%)	
occurrences (all)	10	1	
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
Anal incontinence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Gingival pain			

subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Cheilitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	6 / 20 (30.00%)	4 / 10 (40.00%)	
occurrences (all)	8	5	
Diarrhoea			
subjects affected / exposed	8 / 20 (40.00%)	5 / 10 (50.00%)	
occurrences (all)	11	10	
Dry mouth			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Dysphagia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Aphthous ulcer			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Oral pain			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	9 / 20 (45.00%)	3 / 10 (30.00%)	
occurrences (all)	14	4	
Mouth haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	9 / 20 (45.00%)	2 / 10 (20.00%)	
occurrences (all)	21	2	
Flatulence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pancreatitis			

subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	7 / 20 (35.00%)	3 / 10 (30.00%)	
occurrences (all)	11	7	
Toothache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Steatohepatitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypertransaminasaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 20 (5.00%)	2 / 10 (20.00%)	
occurrences (all)	5	2	
Pruritus			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Rash maculo-papular			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Dermatitis contact			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Alopecia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Scab			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Skin atrophy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Hyperhidrosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Dermatitis acneiform			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Pain of skin			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Erythemas			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Pollakiuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Dysuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	

Haematuria			
subjects affected / exposed	6 / 20 (30.00%)	4 / 10 (40.00%)	
occurrences (all)	6	5	
Proteinuria			
subjects affected / exposed	10 / 20 (50.00%)	8 / 10 (80.00%)	
occurrences (all)	23	15	
Micturition urgency			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Renal tubular dysfunction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Glycosuria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Urinary tract pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Urinary retention			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	8 / 20 (40.00%)	2 / 10 (20.00%)	
occurrences (all)	14	3	
Hyperparathyroidism			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			

subjects affected / exposed	5 / 20 (25.00%)	2 / 10 (20.00%)	
occurrences (all)	7	2	
Neck pain			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Myalgia			
subjects affected / exposed	4 / 20 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	6	5	
Muscular weakness			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	2	
Back pain			
subjects affected / exposed	4 / 20 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	6	1	
Arthralgia			
subjects affected / exposed	6 / 20 (30.00%)	3 / 10 (30.00%)	
occurrences (all)	11	5	
Joint range of motion decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Spinal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Pain in jaw			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Periostitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Myositis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			

subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Otitis media			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infections			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Otitis media acute			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Device related infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	

Urinary tract infection			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 20 (30.00%)	2 / 10 (20.00%)	
occurrences (all)	9	3	
Hypermagnesaemia			
subjects affected / exposed	3 / 20 (15.00%)	2 / 10 (20.00%)	
occurrences (all)	6	4	
Hyperkalaemia			
subjects affected / exposed	4 / 20 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Hypercalcaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	4 / 20 (20.00%)	2 / 10 (20.00%)	
occurrences (all)	6	2	
Dehydration			
subjects affected / exposed	4 / 20 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	5	2	
Hypertriglyceridaemia			
subjects affected / exposed	12 / 20 (60.00%)	5 / 10 (50.00%)	
occurrences (all)	26	18	
Hypomagnesaemia			

subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	3	2	
Hypokalaemia			
subjects affected / exposed	2 / 20 (10.00%)	4 / 10 (40.00%)	
occurrences (all)	2	6	
Hypocholesterolaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	4 / 20 (20.00%)	5 / 10 (50.00%)	
occurrences (all)	6	7	
Hypoalbuminaemia			
subjects affected / exposed	4 / 20 (20.00%)	5 / 10 (50.00%)	
occurrences (all)	14	13	
Hyponatraemia			
subjects affected / exposed	2 / 20 (10.00%)	7 / 10 (70.00%)	
occurrences (all)	3	15	
Hypophosphataemia			
subjects affected / exposed	6 / 20 (30.00%)	8 / 10 (80.00%)	
occurrences (all)	10	14	
Hypoglycaemia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Hyperphosphataemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2018	Protocol amendment 01: Figure 1 study design updated; Reduced maximum number of subjects in the dose levels -1, 1, 2 and 3 to 54 subjects in Phase 1 and 120 subjects in Phase 1 and 2. The projected maximum number of evaluable subjects required in Phase 1 was recalculated to 48 subjects; Study treatment should be discontinued in any subject who develops gastrointestinal perforation or life threatening fistula.
28 April 2020	Protocol amendment 02: It was clarified that sponsor will closely monitor enrollment to ensure that at least 50% of subjects enrolled in each cohort are <18 years of age at the time of informed consent; Clarified that lenvatinib should be discontinued in any subject who develops gastrointestinal perforation of any grade or >=grade 4 fistula; Clarified that for CTCAE, version 4.03 will be used and not current version.
16 August 2021	Protocol amendment 03: Evaluable analysis set, defined as all subjects who have measurable disease present at baseline and at least one post-baseline efficacy assessment, unless they have discontinued prior to first efficacy assessment due to progressive disease. This will be analysis set for efficacy in Phase 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported