Clinical trial results:
Phase 2 Trial of XL184 (Cabozantinib) an Oral Small-Molecule Inhibitor of Multiple Kinases, in Children and Young Adults with Refractory Sarcomas, Wilms Tumor, and Other Rare Tumors

Summary

EudraCT number	2019-001238-32
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	ADVL1622

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02867592
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Cancer Institute Cancer Therapy Evaluation Program (NCI/CTEP)
Sponsor organisation address	9609 Medical Center Drive, Bethesda, MD, United States, 20892
Public contact	Medical Director, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001143-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	30 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2021
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

• To determine the objective response rate (ORR) (complete response [CR] + partial response [PR]) of cabozantinib in children and young adults with Ewing sarcoma, rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), Wilms tumor and other rare tumors.
• To estimate whether cabozantinib therapy either improves the disease control rate at 4 months in subjects with recurrent or refractory measurable osteosarcoma as compared to a historical Children's Oncology Group (COG) experience or produces an ORR.

Protection of trial subjects:

The study was conducted in accordance with National Cancer Institute (NCI) standards, policies and procedures of NCI and the COG and in accordance with applicable laws. COG is an NCI supported National Clinical Trials Network group. The study was conducted according to the ethical principles of the Declaration of Helsinki. This study was conducted in accordance with all applicable regulatory requirements according to the policies and procedures of NCI and COG.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 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: 109
Worldwide total number of subjects	109
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)	27
Adolescents (12-17 years)	44
Adults (18-64 years)	38
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This open label 2-stage Phase 2 trial was conducted to assess the activity of cabozantinib in children and young adults in the following disease strata: non-osteosarcoma, osteosarcoma and other rare tumors.

Pre-assignment

Screening details:

A total of 109 subjects were enrolled into the study at 53 study centers, of whom of 108 subjects received at least one dose of cabozantinib. Here, results for data analyzed through data cut-off 30-Jun-2021 has been reported.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Osteosarcoma

Arm description:

Subjects diagnosed with recurrent or refractory measurable osteosarcoma who have had histologic verification at original diagnosis or at relapse, were enrolled into the osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 milligrams per meter squared per day (mg/m^2/day) (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram), with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	XL184
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received cabozantinib 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram). Drug doses were adjusted based on the body surface area (BSA) calculated from height and actual body weight measured within 7 days before the beginning of each cycle.

Arm title	Non-osteosarcoma

Arm description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification for one of the following malignancies at original diagnosis or at relapse: Ewing sarcoma, RMS, NRSTS, or Wilms tumor, were enrolled into the non-osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Cabozantinib
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Dosage and administration details:

Subjects received cabozantinib 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram). Drug doses were adjusted based on the BSA calculated from height and actual body weight measured within 7 days before the beginning of each cycle.

Arm title	All Rare Tumors

Arm description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification of one of the following malignancies at original diagnosis or at relapse: medullary thyroid carcinoma, renal cell carcinoma, hepatocellular carcinoma, hepatoblastoma, adrenocortical carcinoma or other rare solid tumors, were enrolled into the rare tumor stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Arm type	Experimental
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Dosage and administration details:

Subjects received cabozantinib 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram). Drug doses were adjusted based on the BSA calculated from height and actual body weight measured within 7 days before the beginning of each cycle.

Number of subjects in period 1[1]	Osteosarcoma	Non-osteosarcoma	All Rare Tumors
Started	29	54	25
Completed	6	12	5
Not completed	23	42	20
Consent withdrawn by subject	1	1	-
Subject enrolled onto another study	2	1	-
Death	20	40	20

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Subject disposition is based on the safety population which included all subjects enrolled and who received at least one dose of cabozantinib. One enrolled subject with Ewing sarcoma (non-osteosarcoma strata) did not receive study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Osteosarcoma

Reporting group description:

Subjects diagnosed with recurrent or refractory measurable osteosarcoma who have had histologic verification at original diagnosis or at relapse, were enrolled into the osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 milligrams per meter squared per day (mg/m^2/day) (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram), with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Reporting group title	Non-osteosarcoma

Reporting group description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification for one of the following malignancies at original diagnosis or at relapse: Ewing sarcoma, RMS, NRSTS, or Wilms tumor, were enrolled into the non-osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Reporting group title	All Rare Tumors

Reporting group description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification of one of the following malignancies at original diagnosis or at relapse: medullary thyroid carcinoma, renal cell carcinoma, hepatocellular carcinoma, hepatoblastoma, adrenocortical carcinoma or other rare solid tumors, were enrolled into the rare tumor stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Reporting group values	Osteosarcoma	Non-osteosarcoma	All Rare Tumors
Number of subjects	29	54	25
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)	5	12	10
Adolescents (12-17 years)	12	19	12
Adults (18-64 years)	12	23	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	15.8	16.6	12.9
standard deviation	± 3.6	± 5.9	± 3.7
Gender categorical Units: Subjects			
Female	10	27	15
Male	19	27	10

Race Units: Subjects			
Asian	1	5	2
Black Or African American	6	6	2
Multiple	0	1	0
Native Hawaiian Or Other Pacific Islander	1	0	1
Not Reported	2	2	2
Unknown	3	5	4
White	16	35	14
Ethnicity Units: Subjects			
Hispanic Or Latino	8	5	8
Not Hispanic Or Latino	20	47	15
Not Reported	1	1	1
Unknown	0	1	1
BSA Units: Meters^2			
arithmetic mean	1.561	1.564	1.415
standard deviation	± 0.338	± 0.400	± 0.359

Reporting group values	Total		
Number of subjects	108		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	27		
Adolescents (12-17 years)	43		
Adults (18-64 years)	38		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	52		
Male	56		
Race Units: Subjects			
Asian	8		
Black Or African American	14		
Multiple	1		
Native Hawaiian Or Other Pacific Islander	2		
Not Reported	6		
Unknown	12		

White	65		
Ethnicity Units: Subjects			
Hispanic Or Latino	21		
Not Hispanic Or Latino	82		
Not Reported	3		
Unknown	2		
BSA Units: Meters^2 arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Osteosarcoma

Reporting group description:

Subjects diagnosed with recurrent or refractory measurable osteosarcoma who have had histologic verification at original diagnosis or at relapse, were enrolled into the osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 milligrams per meter squared per day (mg/m^2/day) (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram), with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Reporting group title	Non-osteosarcoma

Reporting group description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification for one of the following malignancies at original diagnosis or at relapse: Ewing sarcoma, RMS, NRSTS, or Wilms tumor, were enrolled into the non-osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Reporting group title	All Rare Tumors

Reporting group description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification of one of the following malignancies at original diagnosis or at relapse: medullary thyroid carcinoma, renal cell carcinoma, hepatocellular carcinoma, hepatoblastoma, adrenocortical carcinoma or other rare solid tumors, were enrolled into the rare tumor stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Subject analysis set title	Overall - All Strata
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were enrolled into the osteosarcoma, non-osteosarcoma and rare tumor strata are included in this group. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Primary: Objective Response Rate: All Strata

End point title	Objective Response Rate: All Strata[1]

End point description:

The ORR was defined as the percentage of subjects who achieved either CR or PR according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria. Evaluable Population for Response included all eligible subjects who had an answer equal to 'Yes' at the question 'Is the subject evaluable for response assessment?' from the case report form (CRF) page.

End point type	Primary

End point timeframe:

From first date of cabozantinib intake up to 6 months

Notes:

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

End point values	Osteosarcoma	Non-osteosarcoma	All Rare Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	52	23	
Units: percentage of subjects				
number (confidence interval 95%)	6.9 (0.8 to 22.8)	0 (0.0 to 6.8)	13.0 (2.8 to 33.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Disease Control Rate: Osteosarcoma Stratum

End point title	Disease Control Rate: Osteosarcoma Stratum[2][3]

End point description:

Disease control rate is the rate of subjects with disease control success defined as subjects with a best overall CR, PR or stable disease (SD) after 4 months of therapy or at the end of the sixth cycle, whichever occured first. DCR was assessed only in the osteosarcoma stratum. Evaluable Population for Response included all eligible subjects who had an answer equal to 'Yes' at the question 'Is the subject evaluable for response assessment?' from the CRF page.

End point type	Primary

End point timeframe:

From first date of cabozantinib intake up to 4 months or end of sixth cycle, whichever occured first

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 additional statistical analysis was pre-specified for this 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: Only subjects from the osteosarcoma stratum arm were analyzed for this primary endpoint.

End point values	Osteosarcoma			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percentage of subjects				
number (confidence interval 95%)	34.5 (17.9 to 54.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP): All Strata

End point title	Time to Progression (TTP): All Strata

End point description:

TTP corresponds to the time where subjects are still in the study without progressive disease (PD) as the overall disease response. 1-year TTP was calculated from the first cabozantinib intake date up to the

date of the first overall disease response showing PD (during treatment cycles or follow-up visits) within 1-year of follow-up. 1-year of follow-up was defined as the lapse time between the first cabozantinib intake date and the first cabozantinib date + 365.25 days. Evaluable Population for Response included all eligible subjects who had an answer equal to 'Yes' at the question 'Is the subject evaluable for response assessment?' from the CRF page.

End point type	Secondary

End point timeframe:

Up to 1 year after the first cabozantinib intake date

End point values	Osteosarcoma	Non-osteosarcoma	All Rare Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	52	23	
Units: months				
median (confidence interval 95%)	4.6 (2.1 to 6.6)	3.3 (1.9 to 4.0)	5.3 (1.8 to 7.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS): All Strata

End point title	Progression Free Survival (PFS): All Strata

End point description:

PFS was calculated from the first cabozantinib intake date until the date of the first documented PD or date of death due to any cause if no progression was recorded before. Evaluable Population for Response included all eligible subjects who had an answer equal to 'Yes' at the question 'Is the subject evaluable for response assessment?' from the CRF page.

End point type	Secondary

End point timeframe:

From first date of cabozantinib intake until the date of first documented progression or date of death from any cause, whichever came first; assessed up to data cut-off (overall timeframe of approximately up to 4 years)

End point values	Osteosarcoma	Non-osteosarcoma	All Rare Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	52	23	
Units: months				
median (confidence interval 95%)	4.6 (2.1 to 6.0)	2.9 (1.8 to 4.0)	4.2 (1.8 to 5.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): All Strata

End point title	Overall Survival (OS): All Strata

End point description:

The OS was defined as the duration between the date of first cabozantinib intake and the date of death. Evaluable Population for Response included all eligible subjects who had an answer equal to 'Yes' at the question 'Is the subject evaluable for response assessment?' from the CRF page.

End point type	Secondary

End point timeframe:

From first date of cabozantinib intake until date of death; assessed up to data cut-off (overall timeframe of approximately up to 4 years)

End point values	Osteosarcoma	Non-osteosarcoma	All Rare Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	52	23	
Units: months				
median (confidence interval 95%)	9.3 (6.3 to 12.2)	13.1 (5.3 to 14.3)	9.0 (5.2 to 12.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cabozantinib Plasma Concentrations: All Strata

End point title	Cabozantinib Plasma Concentrations: All Strata

End point description:

Blood samples were collected at pre-specified timepoints and plasma concentrations of cabozantinib were measured by liquid chromatography tandem mass spectroscopy method. Evaluable Population for Pharmacokinetic (PK) included subjects who consented to participate in the PK portion of the study, and who received cabozantinib on Cycle 1 Day 1 and had at least one plasma cabozantinib concentration.

End point type	Secondary

End point timeframe:

Cycle (C)1 Pre-dose and 2-4 hours post-dose on Day 22. Each cycle lasted for 28 days.

End point values	Overall - All Strata			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: nanograms / milliliter				
arithmetic mean (standard deviation)				
C1 Pre-dose, Day 22	1277.5 (± 654.2)			
C1 2-4 hours post-dose Day 22	1764.9 (± 871.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are collected from first date of cabozantinib intake until data cut-off (overall timeframe of approximately 4 years)

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as adverse events (AEs) that occurred after the first dose of cabozantinib and up to 30 days after the last dose of cabozantinib. All deaths data reported for treatment-emergent only. The safety population included all enrolled subjects, who received at least one dose of cabozantinib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Osteosarcoma

Reporting group description:

Subjects diagnosed with recurrent or refractory measurable osteosarcoma who have had histologic verification at original diagnosis or at relapse, were enrolled into the osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Reporting group title	Non-osteosarcoma

Reporting group description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification for one of the following malignancies at original diagnosis or at relapse: Ewing sarcoma, RMS, NRSTS, or Wilms tumor, were enrolled into the non-osteosarcoma stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Reporting group title	All Rare Tumors

Reporting group description:

Subjects diagnosed with recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life, and who have had histologic verification of one of the following malignancies at original diagnosis or at relapse: medullary thyroid carcinoma, renal cell carcinoma, hepatocellular carcinoma, hepatoblastoma, adrenocortical carcinoma or other rare solid tumors, were enrolled into the rare tumor stratum. Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram) with no rest period between cycles. Treatment continued until tumor progression or unacceptable toxicity.

Serious adverse events	Osteosarcoma	Non-osteosarcoma	All Rare Tumors
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 29 (27.59%)	18 / 54 (33.33%)	11 / 25 (44.00%)
number of deaths (all causes)	20	40	20
number of deaths resulting from adverse events	1	4	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			

subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Non-cardiac chest pain			
subjects affected / exposed	1 / 29 (3.45%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Face oedema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Fatigue			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	2 / 29 (6.90%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)	3 / 54 (5.56%)	0 / 25 (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
Hypoxia			
subjects affected / exposed	0 / 29 (0.00%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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

Oropharyngeal pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Productive cough			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Rhinorrhoea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	3 / 25 (12.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Weight decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigation abnormal			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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

Left ventricular dysfunction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 29 (3.45%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Dysaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Headache			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Paraesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	0 / 25 (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
Eye infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Sepsis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperammonaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Osteosarcoma	Non-osteosarcoma	All Rare Tumors
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 29 (58.62%)	27 / 54 (50.00%)	14 / 25 (56.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 29 (6.90%)	3 / 54 (5.56%)	3 / 25 (12.00%)
occurrences (all)	2	3	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 29 (3.45%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Gait disturbance			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Investigations			
Lipase increased			
subjects affected / exposed	2 / 29 (6.90%)	8 / 54 (14.81%)	0 / 25 (0.00%)
occurrences (all)	2	10	0
Neutrophil count decreased			
subjects affected / exposed	2 / 29 (6.90%)	4 / 54 (7.41%)	4 / 25 (16.00%)
occurrences (all)	2	5	7
Alanine aminotransferase increased			
subjects affected / exposed	1 / 29 (3.45%)	3 / 54 (5.56%)	4 / 25 (16.00%)
occurrences (all)	1	3	4
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 29 (10.34%)	2 / 54 (3.70%)	3 / 25 (12.00%)
occurrences (all)	3	2	3
Weight decreased			
subjects affected / exposed	1 / 29 (3.45%)	4 / 54 (7.41%)	0 / 25 (0.00%)
occurrences (all)	1	4	0
Platelet count decreased			
subjects affected / exposed	0 / 29 (0.00%)	3 / 54 (5.56%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 29 (0.00%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	0	4	0
White blood cell count decreased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 54 (3.70%)	1 / 25 (4.00%)
occurrences (all)	1	2	1
Amylase increased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Blood bilirubin increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	5	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Urine output decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	2 / 29 (6.90%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			

Angina pectoris			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hemiparesis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	3 / 25 (12.00%)
occurrences (all)	0	2	3
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	4 / 54 (7.41%)	1 / 25 (4.00%)
occurrences (all)	2	5	1
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	2	3	0
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	1	4	0
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pancreatitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 29 (3.45%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Skin exfoliation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 29 (6.90%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Back pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Decreased appetite			
subjects affected / exposed	1 / 29 (3.45%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Dehydration			
subjects affected / exposed	0 / 29 (0.00%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Hyponatraemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Hypophosphataemia			

subjects affected / exposed	1 / 29 (3.45%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	2	1	0
Hypernatraemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2018	•Osteosarcoma was included in the list of solid tumor strata being studied. •Rearranged during transfection rearrangement mutation was added to the list of rare tumor molecular alterations. •A primary aim to estimate whether cabozantinib therapy improves the DCR at 4 months in subjects with recurrent or refractory measurable osteosarcoma compared to a historical COG experience or produces an ORR was added to reflect the addition of the osteosarcoma group. •A secondary aim to estimate 1-year TTP, PFS and OS for each stratum, and if feasible to compare to historical controls was added. •The rationale for adding the osteosarcoma disease cohort was added. •Osteosarcoma was added to the list of eligible diagnoses for enrolment into the study. •The eligibility criteria regarding anti-cancer agents, antibody doses, alanine aminotransferase, blood pressure control were updated. •A recommendation to use caution and monitor AE when administering cabozantinib with multidrug resistance-associated protein inhibitors was added. •Guidelines to monitor the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave corrected (QTc) after taking concomitant medications with risk of prolonged QTc were added. •The cumulative weekly dose was set at 280 mg/m^2. •Dose-limiting hypertension definition was revised. •An adult BP criterion for hypertension was added. •Consent to PK collection, additional PK, defining PK evaluability and evaluation of PK parameters sampling was added. •Long term stable disease was defined. •Subject not receiving protocol treatment after study enrolment was added as an off-study criterion. •Sample size, stratum-specific study design and study duration estimates for the osteosarcoma group were added. •New disease control response criteria specifically for the osteosarcoma group were added.
18 July 2018	•The version number of common terminology criteria for adverse events was updated from version 4 to version 5. •Definition of central nervous system function inclusion criterion was updated. •Non-hematological dose-limiting toxicity was updated to clarify the upper limit of normal range for aspartate aminotransferase, dosing tables were clarified to account for a different start day other than Monday. •Definition of neonatal death was updated. •Expediting reporting was updated to include pregnancy loss.
16 April 2019	The cabozantinib Comprehensive Adverse Events and Potential Risks was updated per the guidelines in the Rapid Request for Amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Results reported are based on data cutoff of 30-Jun-2021.

Notes: