Clinical trial results:
A Phase II study of XL 184 (Cabozantinib) in treating patients with relapsed Osteosarcomas and Ewing Sarcomas.

Summary

EudraCT number	2014-004407-71
Trial protocol	FR
Global end of trial date	30 June 2019

Results information

Result version number	v1 (current)
This version publication date	03 January 2024
First version publication date	03 January 2024
Summary attachment (see zip file)	Italiano et al. 2020 (Italiano 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	IB2014-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02243605
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Bergonié
Sponsor organisation address	229 cours de l'Argonne, Bordeaux, France, 33076
Public contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr
Scientific contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2019
Global end of trial reached?	Yes
Global end of trial date	30 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor activity of cabozantinib in terms of :
•Osteosarcoma: 6-month non-progression (Complete response, partial response and stable disease) and 6-month objective response (Complete response, partial response) rates (composite endpoint) as per the Response Evaluation Criteria in Solid Tumors, Revised RECIST v1.1.
•Ewing sarcoma: 6-month objective response as per the revised RECIST v1.1.

Protection of trial subjects:

The study will be carried out in accordance with:
- The ethical principles of the current version of the "Declaration of Helsinki"
- Good Clinical Practice (GCP): I.C.H. version 4 of 1 May 1996 and decision dated 24 November 2006 (Official Bulletin of 30 November 2006, text 64).
- European Directive (2001/20/EC) on clinical trial procedures.
- Huriet's law (No. 88-1138) dated 20 December 1988, concerning the protection of persons taking part in Biomedical Research with the provisions of the Public Health law (No. 2004-806) of 9 August 2004 and implementating decree No. 2006-477 of 26 April 2006 relating to biomedical research.
- The French law on Data Protection and Civil Liberties, No. 78-17 of 6 January 1978 amended by law No. 2004-801, dated 6 August 2004, concerning the protection of persons with regards to the processing of personal data.
- The application of Circular DHOS/INCa/MOPRC/2006/475 of 7 November 2006: the Sponsor shall undertake to register the Trial and thus make it accessible to the general public, in the INCa (French Cancer Institute) register via the Internet site: www.e-cancer.fr. Each trial published in the INCa register will be sent to the NCI for registering on the following site: www.clinicaltrials.gov. The trial will be registered before the first patient is entered into the study. The Sponsor is responsible for updating the study data in order to guarantee the reliability of the information available on-line.
- Law no. 2004-800 dated 6 August 2004, concerning bioethics, amended by law No. 2012-387, dated 22 March 2012.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2015
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	France: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	0
Adolescents (12-17 years)	8
Adults (18-64 years)	74
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Osteosarcoma stratum : During 2 years and 10 months, in France 45 patients were included from 3th of April 2015 to 1st of February 2018.
Ewing stratum : During 3 years and 3 months, in France 45 patients were included from 16th of April 2015 to 12th of July 2018.

Pre-assignment

Screening details:

Osteosarcoma stratum: 67 patients were screened and 45 were included.
Ewing stratum: 58 patients were screened and 45 were included.

Period 1

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

Blinding implementation details:

No blinding used.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cabozantinib - Stratum Osteosarcoma

Arm description:

Single arm treatment - stratum osteosarcoma :
Formulation: XL 184 (Cabozantinib) – Available in 20 mg and 60 mg tablet. Tablets are yellow film coated. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.
Route of administration: Oral
Administered dose: to take without food , and not eat for at least 2 hours before and 1 hour after taking it:
- for patients ≥16 years: 60 mg
- For patients ≥12 years < 16 years: 40 mg/m² (Chuck et al., 2014)
Treatment schedule: Daily, day 1-28 during 4 weeks (ie. 1 cycle)

Arm type	Experimental
Investigational medicinal product name	XL184 (CABOZANTINIB) (NSC 761968)
Investigational medicinal product code	XL184 (CABOZANTINIB) (NSC 761968)
Other name	Cabozantinib, EXEL-7184, EXEL-02977184
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib is supplied by Exelixis and distributed by CSM (Clinical Supplies Management Europe GmbH) in Germany. Cabozantinib is available in 20 mg and 60 mg tablet. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.

Arm title	Cabozantinib - Stratum Ewing

Arm description:

Single arm treatment - stratum ewing :
Formulation: XL 184 (Cabozantinib) – Available in 20 mg and 60 mg tablet. Tablets are yellow film coated. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.
Route of administration: Oral
Administered dose: to take without food , and not eat for at least 2 hours before and 1 hour after taking it:
- for patients ≥16 years: 60 mg

- For patients ≥12 years < 16 years: 40 mg/m² (Chuck et al., 2014)
Treatment schedule: Daily, day 1-28 during 4 weeks (ie. 1 cycle)

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Number of subjects in period 1	Cabozantinib - Stratum Osteosarcoma	Cabozantinib - Stratum Ewing
Started	45	45
Completed	42	39
Not completed	3	6
Did not receive at least one complete or two incom	2	1
Not meeting eligibility criteria	1	5

Baseline characteristics

Reporting groups

Reporting group title	Cabozantinib - Stratum Osteosarcoma

Reporting group description:

Single arm treatment - stratum osteosarcoma :
Formulation: XL 184 (Cabozantinib) – Available in 20 mg and 60 mg tablet. Tablets are yellow film coated. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.
Route of administration: Oral
Administered dose: to take without food , and not eat for at least 2 hours before and 1 hour after taking it:
- for patients ≥16 years: 60 mg
- For patients ≥12 years < 16 years: 40 mg/m² (Chuck et al., 2014)
Treatment schedule: Daily, day 1-28 during 4 weeks (ie. 1 cycle)

Reporting group title	Cabozantinib - Stratum Ewing

Reporting group description:

Single arm treatment - stratum ewing :
Formulation: XL 184 (Cabozantinib) – Available in 20 mg and 60 mg tablet. Tablets are yellow film coated. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.
Route of administration: Oral
Administered dose: to take without food , and not eat for at least 2 hours before and 1 hour after taking it:
- for patients ≥16 years: 60 mg
- For patients ≥12 years < 16 years: 40 mg/m² (Chuck et al., 2014)
Treatment schedule: Daily, day 1-28 during 4 weeks (ie. 1 cycle)

Reporting group values	Cabozantinib - Stratum Osteosarcoma	Cabozantinib - Stratum Ewing	Total
Number of subjects	45	45	90
Age categorical Units: Subjects			
<= 18 years	7	6	13
19-64 years	31	38	69
>= 65 years	7	1	8
Age continuous Units: years			
arithmetic mean	38.0	35.7	
standard deviation	± 19.3	± 14.7	-
Gender categorical Units: Subjects			
Female	18	14	32
Male	27	31	58
ECOG			
ECOG PERFORMANCE STATUS ASSESSMENT SCALE: 0: Normal activity. Fully active able to carry on all pre-disease performance without restriction. 1: Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature. 2: In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. 3: In bed >50% of the time. Capable of only limited self-care confined to bed or chair more than 50% of of waking hours.			
Units: Subjects			
ECOG = 0	17	15	32
ECOG =1	25	29	54

ECOG =2	1	1	2
ECOG = 3	1	0	1
Not available	1	0	1

End points

End points reporting groups

Reporting group title	Cabozantinib - Stratum Osteosarcoma

Reporting group description:

Single arm treatment - stratum osteosarcoma :
Formulation: XL 184 (Cabozantinib) – Available in 20 mg and 60 mg tablet. Tablets are yellow film coated. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.
Route of administration: Oral
Administered dose: to take without food , and not eat for at least 2 hours before and 1 hour after taking it:
- for patients ≥16 years: 60 mg
- For patients ≥12 years < 16 years: 40 mg/m² (Chuck et al., 2014)
Treatment schedule: Daily, day 1-28 during 4 weeks (ie. 1 cycle)

Reporting group title	Cabozantinib - Stratum Ewing

Reporting group description:

Single arm treatment - stratum ewing :
Formulation: XL 184 (Cabozantinib) – Available in 20 mg and 60 mg tablet. Tablets are yellow film coated. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.
Route of administration: Oral
Administered dose: to take without food , and not eat for at least 2 hours before and 1 hour after taking it:
- for patients ≥16 years: 60 mg
- For patients ≥12 years < 16 years: 40 mg/m² (Chuck et al., 2014)
Treatment schedule: Daily, day 1-28 during 4 weeks (ie. 1 cycle)

Primary: Non progression at 6 months

End point title	Non progression at 6 months[1]

End point description:

Efficacy of Cabozantinib will be assessed in terms of 6-month non-progression and objective response within 6 months of treatment onset (dual endpoint design). More precisely, progression has to be assessed at 6 months and objective response has to be assessed within 6 months of treatment onset.
- Non-progression is defined as complete response, partial response or stable disease (RECIST 1.1).

End point type	Primary

End point timeframe:

at 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 statistical analysis planned.
Osteosarcoma : Primary based on the rate of objective response within 6 months of treatment onset will be reported based on an optimal two-stage Simon’s design.
Ewing sarcoma : Secondary endpoint

End point values	Cabozantinib - Stratum Osteosarcoma	Cabozantinib - Stratum Ewing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[2]	39		
Units: subjects	17	10		

Notes:

[2] - 45 patients had been included
o 42 were eligible and assessable for efficacy

Attachments (see zip file)	Table : non progression at 6 months/Capture.PNG

Statistical analyses

No statistical analyses for this end point

Primary: Objective response within 6 months of treatment onset rate

End point title	Objective response within 6 months of treatment onset rate[3]

End point description:

Efficacy of Cabozantinib will be assessed in terms objective response within 6 months of treatment onset. More precisely, objective response has to be assessed within 6 months of treatment onset.
- Objective response is defined as complete response or partial response (RECIST 1.1).

End point type	Primary

End point timeframe:

at 6 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis planned.
Osteosarcoma : Secondary endpoint
Ewing sarcoma : Primary based on the rate of objective response within 6 months of treatment onset will be reported based on an optimal two-stage Simon's design.

End point values	Cabozantinib - Stratum Osteosarcoma	Cabozantinib - Stratum Ewing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39[4]		
Units: Subjects	5	10		

Notes:

[4] - 45 patients had been included
o 39 were eligible and assessable for efficacy

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response: RECIST 1.1 with confirmation required

End point title	Best overall response: RECIST 1.1 with confirmation required

End point description:

Best overall response according to RECIST 1.1 with confirmation required include confirmation for complete response (CR), partial response (PR) and stable disease (SD).

End point type	Secondary

End point timeframe:

Best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

End point values	Cabozantinib - Stratum Osteosarcoma	Cabozantinib - Stratum Ewing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: Subjects				
Partial response	3	5		
Stable disease	21	19		
Progressive disease	15	12		
Not evaluable	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS will be assessed on the population eligible and assessable for efficacy. PFS will be analysed using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

End point values	Cabozantinib - Stratum Osteosarcoma	Cabozantinib - Stratum Ewing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: months				
median (confidence interval 95%)	5.9 (4.7 to 7.4)	4.4 (3.7 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS will be assessed on the population eligible and assessable for efficacy criteria. OS will be analyzed using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Overall survival (OS) is defined as the duration of time from start of treatment to the time of death.

End point values	Cabozantinib - Stratum Osteosarcoma	Cabozantinib - Stratum Ewing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: months				
median (confidence interval 95%)	10.4 (7.4 to 12.5)	12.5 (8.5 to 20.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety profile will be continuously followed during treatment and up to 30 days after the last Cabozantinib dose or until the start of a new antitumor therapy, whichever occurs first.

Adverse event reporting additional description:

Adverse event (AE) are reported for all patients who received at least one administration of treatment. All AE and SAE (related and unrelated to treatment) are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Ewing

Reporting group description: -

Reporting group title	Osteosarcoma

Reporting group description: -

Serious adverse events	Ewing	Osteosarcoma	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 45 (66.67%)	31 / 45 (68.89%)	
number of deaths (all causes)	37	42	
number of deaths resulting from adverse events	10	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE TUMORAL PAIN			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST MICROCALCIFICATION PRESENCE			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC PAIN LOCATED ON THE SITE OF THE INITIAL TUMOR			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT LOWER LIMB PAIN			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
WORSENING OF GENERAL STATUS			
subjects affected / exposed	3 / 45 (6.67%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
FATIGUE			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEVER			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THORACIC PAIN			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
BILATERAL PLEURAL EFFUSION			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DYSPNEA			
subjects affected / exposed	2 / 45 (4.44%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
PLEURAL EFFUSION			
subjects affected / exposed	1 / 45 (2.22%)	5 / 45 (11.11%)	
occurrences causally related to treatment / all	0 / 1	1 / 7	
deaths causally related to treatment / all	0 / 1	1 / 2	
PNEUMOPATHY			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIGHT PNEUMOTHORAX			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
EPISTAXIS			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT PNEUMOTHORAX			
subjects affected / exposed	0 / 45 (0.00%)	3 / 45 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	8 / 45 (17.78%)	5 / 45 (11.11%)	
occurrences causally related to treatment / all	11 / 12	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

RIGHT PLEUROPNEUMOPATHY			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOMEDIASTINUM			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILATERAL PNEUMOTHORAX			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RELAPSE OF PNEUMOTHORAX			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
RELAPSE OF PSYCHIATRIC DISORDERS			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
LIPASE INCREASE			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEUTROPENIA			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
WOUND COMPLICATION			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 2	
HYPOCINETIC CARDIOPATHY			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
MEDULLARY COMPRESSION			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
DEFICIT OF LOWER LIMBS			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			

subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PERIPHERAL MOTOR NEUROPATHY			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANEMIA			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HEMORRHAGE			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
ICTERIC CHOLESTASIS			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SACRUM SKIN ULCERATION			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
WORSENING OF SKIN ULCERATION			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
ACUTE RENAL INSUFFISIENCY			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ACUTE BONE PAIN			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
BONE PAIN			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COAST AND LUMBAR PAIN			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
ACUTE OBSTRUCTIVE PYELONEPHRITIS			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL ABSCESS			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS INFECTION			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
FACIAL CELLULITIS			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALIZED INFECTION			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SEPTIC SHOCK			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
DIABETES			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESEMIA			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
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	Ewing	Osteosarcoma	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)	45 / 45 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Tumor pain			
subjects affected / exposed	9 / 45 (20.00%)	9 / 45 (20.00%)	
occurrences (all)	10	11	
Vascular disorders			
Hematoma			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Hot flashes			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	3 / 45 (6.67%)	8 / 45 (17.78%)	
occurrences (all)	3	9	
Hypotension			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Thromboembolic event			
subjects affected / exposed	0 / 45 (0.00%)	5 / 45 (11.11%)	
occurrences (all)	0	5	
Surgical and medical procedures			

Surgical and medical procedures - Other, specify			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Death NOS			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Disease progression			
subjects affected / exposed	4 / 45 (8.89%)	2 / 45 (4.44%)	
occurrences (all)	4	2	
Edema limbs			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Facial pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	34 / 45 (75.56%)	39 / 45 (86.67%)	
occurrences (all)	36	42	
Fever			
subjects affected / exposed	7 / 45 (15.56%)	9 / 45 (20.00%)	
occurrences (all)	9	12	
Flu like symptoms			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
General disorders and administration site conditions - Other, specify			
subjects affected / exposed	4 / 45 (8.89%)	4 / 45 (8.89%)	
occurrences (all)	4	4	
Hypothermia			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Localized edema			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Neck edema			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	5 / 45 (11.11%)	8 / 45 (17.78%)	
occurrences (all)	5	11	
Pain			
subjects affected / exposed	6 / 45 (13.33%)	8 / 45 (17.78%)	
occurrences (all)	6	8	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Gynecomastia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Scrotal pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Vaginal inflammation			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Uterine hemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Bronchial obstruction			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Allergic rhinitis			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Cough			
subjects affected / exposed	11 / 45 (24.44%)	12 / 45 (26.67%)	
occurrences (all)	13	14	
Dyspnea			
subjects affected / exposed	8 / 45 (17.78%)	12 / 45 (26.67%)	
occurrences (all)	8	12	
Epistaxis			
subjects affected / exposed	4 / 45 (8.89%)	9 / 45 (20.00%)	
occurrences (all)	5	9	
Hoarseness			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Pleural effusion			
subjects affected / exposed	3 / 45 (6.67%)	9 / 45 (20.00%)	
occurrences (all)	3	10	
Pleuritic pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Pneumonitis			
subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Pneumothorax			

subjects affected / exposed	11 / 45 (24.44%)	10 / 45 (22.22%)	
occurrences (all)	15	11	
Respiratory, thoracic and mediastinal disorders - Other, specify			
subjects affected / exposed	3 / 45 (6.67%)	6 / 45 (13.33%)	
occurrences (all)	4	6	
Sleep apnea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Rhinorrhea			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Sore throat			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Voice alteration			
subjects affected / exposed	5 / 45 (11.11%)	10 / 45 (22.22%)	
occurrences (all)	5	11	
Wheezing			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 45 (4.44%)	5 / 45 (11.11%)	
occurrences (all)	2	5	
Depression			
subjects affected / exposed	2 / 45 (4.44%)	5 / 45 (11.11%)	
occurrences (all)	2	5	
Insomnia			
subjects affected / exposed	3 / 45 (6.67%)	6 / 45 (13.33%)	
occurrences (all)	3	6	
Psychiatric disorders - Other, specify			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Suicide attempt			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	23 / 45 (51.11%)	21 / 45 (46.67%)	
occurrences (all)	27	25	
Alkaline phosphatase increased			
subjects affected / exposed	7 / 45 (15.56%)	6 / 45 (13.33%)	
occurrences (all)	9	6	
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 45 (48.89%)	23 / 45 (51.11%)	
occurrences (all)	27	28	
Blood bilirubin increased			
subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Blood lactate dehydrogenase increased			
subjects affected / exposed	8 / 45 (17.78%)	10 / 45 (22.22%)	
occurrences (all)	7	7	
CPK increased			
subjects affected / exposed	5 / 45 (11.11%)	1 / 45 (2.22%)	
occurrences (all)	7	1	
Creatinine increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
GGT increased			
subjects affected / exposed	5 / 45 (11.11%)	2 / 45 (4.44%)	
occurrences (all)	5	2	
Hemoglobin increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
INR increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT corrected interval prolonged			

subjects affected / exposed	0 / 45 (0.00%)	4 / 45 (8.89%)	
occurrences (all)	0	4	
Lipase increased			
subjects affected / exposed	6 / 45 (13.33%)	10 / 45 (22.22%)	
occurrences (all)	6	19	
Lymphocyte count decreased			
subjects affected / exposed	5 / 45 (11.11%)	4 / 45 (8.89%)	
occurrences (all)	7	6	
Neutrophil count decreased			
subjects affected / exposed	10 / 45 (22.22%)	9 / 45 (20.00%)	
occurrences (all)	11	11	
Platelet count decreased			
subjects affected / exposed	20 / 45 (44.44%)	14 / 45 (31.11%)	
occurrences (all)	21	16	
Serum amylase increased			
subjects affected / exposed	2 / 45 (4.44%)	4 / 45 (8.89%)	
occurrences (all)	2	4	
Thyroid stimulating hormone increased			
subjects affected / exposed	4 / 45 (8.89%)	6 / 45 (13.33%)	
occurrences (all)	4	6	
Weight loss			
subjects affected / exposed	14 / 45 (31.11%)	15 / 45 (33.33%)	
occurrences (all)	14	15	
White blood cell decreased			
subjects affected / exposed	5 / 45 (11.11%)	4 / 45 (8.89%)	
occurrences (all)	7	6	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Burn			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Fall			

subjects affected / exposed	0 / 45 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	2 / 45 (4.44%)	
occurrences (all)	2	3	
Wound complication			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac disorders - Other, specify			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Heart failure			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Sinus bradycardia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	4 / 45 (8.89%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Nervous system disorders			
Acoustic nerve disorder NOS			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	2	
Dysesthesia			

subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)		
occurrences (all)	2	3		
Dysgeusia				
subjects affected / exposed	15 / 45 (33.33%)	9 / 45 (20.00%)		
occurrences (all)	15	10		
Headache				
subjects affected / exposed	11 / 45 (24.44%)	8 / 45 (17.78%)		
occurrences (all)	12	10		
Nervous system disorders - Other, specify				
subjects affected / exposed	0 / 45 (0.00%)	4 / 45 (8.89%)		
occurrences (all)	0	5		
Neuralgia				
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)		
occurrences (all)	1	2		
Paresthesia				
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)		
occurrences (all)	1	2		
Peripheral motor neuropathy				
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)		
occurrences (all)	0	2		
Peripheral sensory neuropathy				
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)		
occurrences (all)	0	2		
Phantom pain				
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)		
occurrences (all)	0	1		
Somnolence				
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)		
occurrences (all)	0	1		
Spinal cord compression				
subjects affected / exposed	4 / 45 (8.89%)	1 / 45 (2.22%)		
occurrences (all)	4	1		
Tremor				
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)		
occurrences (all)	1	0		

Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	9 / 45 (20.00%)	7 / 45 (15.56%)	
occurrences (all)	10	8	
Febrile neutropenia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Lymph node pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders - Other, specify			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear and labyrinth disorders - Other, specify			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Eye disorders			
Blurred vision			
subjects affected / exposed	4 / 45 (8.89%)	4 / 45 (8.89%)	
occurrences (all)	1	1	
Eye pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, specify			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Periorbital edema			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Photophobia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	

Vision decreased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	12 / 45 (26.67%)	10 / 45 (22.22%)	
occurrences (all)	12	10	
Anal fistula			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Anal mucositis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Bloating			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	2	
Cheilitis			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	15 / 45 (33.33%)	16 / 45 (35.56%)	
occurrences (all)	18	21	
Diarrhea			
subjects affected / exposed	38 / 45 (84.44%)	36 / 45 (80.00%)	
occurrences (all)	51	47	
Dry mouth			
subjects affected / exposed	7 / 45 (15.56%)	1 / 45 (2.22%)	
occurrences (all)	8	1	
Dysphagia			
subjects affected / exposed	4 / 45 (8.89%)	2 / 45 (4.44%)	
occurrences (all)	4	2	
Esophageal pain			

subjects affected / exposed	2 / 45 (4.44%)	2 / 45 (4.44%)	
occurrences (all)	0	0	
Enterocolitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Esophagitis			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Gastroesophageal reflux disease			
subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	
occurrences (all)	8	7	
Flatulence			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	8 / 45 (17.78%)	
occurrences (all)	2	8	
Gastrointestinal pain			
subjects affected / exposed	5 / 45 (11.11%)	3 / 45 (6.67%)	
occurrences (all)	6	3	
Gingival pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Hemorrhoids			
subjects affected / exposed	3 / 45 (6.67%)	2 / 45 (4.44%)	
occurrences (all)	3	2	
Mucositis oral			
subjects affected / exposed	28 / 45 (62.22%)	30 / 45 (66.67%)	
occurrences (all)	31	32	
Nausea			
subjects affected / exposed	16 / 45 (35.56%)	21 / 45 (46.67%)	
occurrences (all)	19	22	
Oral cavity fistula			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	

Oral dysesthesia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Periodontal disease			
subjects affected / exposed	5 / 45 (11.11%)	3 / 45 (6.67%)	
occurrences (all)	6	5	
Rectal hemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Stomach pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	10 / 45 (22.22%)	7 / 45 (15.56%)	
occurrences (all)	12	9	
Hepatobiliary disorders			
Hepatobiliary disorders - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 45 (13.33%)	6 / 45 (13.33%)	
occurrences (all)	6	6	
Dry skin			
subjects affected / exposed	16 / 45 (35.56%)	14 / 45 (31.11%)	
occurrences (all)	17	15	
Eczema			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Erythema multiforme			

subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	
occurrences (all)	3	4	
Hair color changes			
subjects affected / exposed	16 / 45 (35.56%)	18 / 45 (40.00%)	
occurrences (all)	16	18	
Hyperkeratosis			
subjects affected / exposed	2 / 45 (4.44%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	20 / 45 (44.44%)	13 / 45 (28.89%)	
occurrences (all)	21	13	
Pruritus			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Rash acneiform			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Rash maculo-papular			
subjects affected / exposed	1 / 45 (2.22%)	4 / 45 (8.89%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	11 / 45 (24.44%)	22 / 45 (48.89%)	
occurrences (all)	15	31	
Skin hypopigmentation			
subjects affected / exposed	5 / 45 (11.11%)	6 / 45 (13.33%)	
occurrences (all)	5	6	
Skin ulceration			
subjects affected / exposed	2 / 45 (4.44%)	6 / 45 (13.33%)	
occurrences (all)	2	8	
Subcutaneous emphysema			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Telangiectasia			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Chronic kidney disease			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Hematuria			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Proteinuria			
subjects affected / exposed	4 / 45 (8.89%)	8 / 45 (17.78%)	
occurrences (all)	5	9	
Renal and urinary disorders - Other, specify			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Urinary frequency			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Urinary tract obstruction			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Hypothyroidism			
subjects affected / exposed	22 / 45 (48.89%)	23 / 45 (51.11%)	
occurrences (all)	23	25	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 45 (11.11%)	6 / 45 (13.33%)	
occurrences (all)	5	6	
Back pain			
subjects affected / exposed	12 / 45 (26.67%)	8 / 45 (17.78%)	
occurrences (all)	14	8	
Bone pain			
subjects affected / exposed	7 / 45 (15.56%)	2 / 45 (4.44%)	
occurrences (all)	7	2	
Generalized muscle weakness			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Muscle cramp			
subjects affected / exposed	5 / 45 (11.11%)	2 / 45 (4.44%)	
occurrences (all)	5	2	
Muscle weakness lower limb			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorder - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	5 / 45 (11.11%)	
occurrences (all)	2	5	
Myalgia			
subjects affected / exposed	9 / 45 (20.00%)	7 / 45 (15.56%)	
occurrences (all)	9	8	
Neck pain			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Trismus			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Infections and infestations			
Anorectal infection			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Bronchial infection			
subjects affected / exposed	3 / 45 (6.67%)	5 / 45 (11.11%)	
occurrences (all)	4	8	
Catheter related infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Folliculitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Infections and infestations - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	4 / 45 (8.89%)	
occurrences (all)	2	4	
Kidney infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	2 / 45 (4.44%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Otitis externa			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)		
occurrences (all)	0	1		
Paronychia				
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)		
occurrences (all)	1	0		
Penile infection				
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)		
occurrences (all)	0	1		
Pharyngitis				
subjects affected / exposed	4 / 45 (8.89%)	2 / 45 (4.44%)		
occurrences (all)	4	2		
Rhinitis infective				
subjects affected / exposed	1 / 45 (2.22%)	4 / 45 (8.89%)		
occurrences (all)	1	4		
Sepsis				
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)		
occurrences (all)	0	2		
Shingles				
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)		
occurrences (all)	0	1		
Skin infection				
subjects affected / exposed	5 / 45 (11.11%)	1 / 45 (2.22%)		
occurrences (all)	5	1		
Soft tissue infection				
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)		
occurrences (all)	0	2		
Tooth infection				
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)		
occurrences (all)	0	1		
Tracheitis				
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)		
occurrences (all)	1	2		
Upper respiratory infection				
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)		
occurrences (all)	1	1		
Urinary tract infection				

subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	
occurrences (all)	5	3	
Vaginal infection			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Investigations - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	11 / 45 (24.44%)	25 / 45 (55.56%)	
occurrences (all)	13	27	
Hypercalcemia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Hyperglycemia			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Hyperkalemia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Hypoalbuminemia			
subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Hypocalcemia			
subjects affected / exposed	4 / 45 (8.89%)	7 / 45 (15.56%)	
occurrences (all)	5	9	
Hypoglycemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Hypokalemia			
subjects affected / exposed	6 / 45 (13.33%)	11 / 45 (24.44%)	
occurrences (all)	6	14	
Hypomagnesemia			
subjects affected / exposed	7 / 45 (15.56%)	13 / 45 (28.89%)	
occurrences (all)	9	19	

Hyponatremia			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Hypophosphatemia			
subjects affected / exposed	18 / 45 (40.00%)	11 / 45 (24.44%)	
occurrences (all)	23	12	
Metabolism and nutrition disorders - Other, specify			
subjects affected / exposed	2 / 45 (4.44%)	1 / 45 (2.22%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported