



Clinical trial results:

Multicenter, triple-arm, single-stage, phase II trial to determine the preliminary efficacy and safety of RAD001 in patients with histological evidence of progressive or metastatic bone or soft tissue sarcomas

Summary

EudraCT number	2007-005294-60
Trial protocol	DE IT
Global end of trial date	17 May 2017

Results information

Result version number	v1 (current)
This version publication date	30 May 2018
First version publication date	30 May 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001C24114
-----------------------	---------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00767819
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

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	17 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to evaluate the preliminary efficacy of everolimus in progressive or metastatic bone and soft tissue sarcoma for each of the 3 indication arms separately. Efficacy was defined as the proportion of patients showing complete response (CR), partial response (PR) or stable disease (SD) at 16 weeks (as best overall response) according to RECIST

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 61
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	71
EEA total number of subjects	71

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)	0
Adults (18-64 years)	54
From 65 to 84 years	17

85 years and over	0
-------------------	---

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Seventy-four patients were screened and seventy-one enrolled.

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	Arm 1
------------------	-------

Arm description:

Progressive or metastatic bone or soft tissue sarcomas

Arm type	Experimental
Investigational medicinal product name	everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose for all patients was everolimus 10 mg/day orally; this daily dose could be stepwise reduced by 2 dose levels to 5 mg/day or 5 mg every other day in the event of intolerance

Arm title	Arm 2
------------------	-------

Arm description:

Progressive gastrointestinal stromal tumors (GIST) after failure of prior imatinib and sunitinib 1st and 2nd line

Arm type	Experimental
Investigational medicinal product name	everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose for all patients was everolimus 10 mg/day orally; this daily dose could be stepwise reduced by 2 dose levels to 5 mg/day or 5 mg every other day in the event of intolerance

Arm title	Arm 3
------------------	-------

Arm description:

Progressive or metastatic alveolar soft part sarcoma (ASPS)

Arm type	Experimental
Investigational medicinal product name	everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose for all patients was everolimus 10 mg/day orally; this daily dose could be stepwise reduced by 2 dose levels to 5 mg/day or 5 mg every other day in the event of intolerability

Number of subjects in period 1	Arm 1	Arm 2	Arm 3
Started	37	24	10
Intent to treat (ITT) analysis set	37	24	10
Safety analysis set (SAF)	37	24	10
Completed	12	5	10
Not completed	25	19	0
Adverse event, serious fatal	2	3	-
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	2	-	-
Unsatisfactory therapeutic effect	18	14	-
Administrative problems	-	1	-
Abnormal lab values	1	-	-
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Arm 1
Reporting group description:	
Progressive or metastatic bone or soft tissue sarcomas	
Reporting group title	Arm 2
Reporting group description:	
Progressive gastrointestinal stromal tumors (GIST) after failure of prior imatinib and sunitinib 1st and 2nd line	
Reporting group title	Arm 3
Reporting group description:	
Progressive or metastatic alveolar soft part sarcoma (ASPS)	

Reporting group values	Arm 1	Arm 2	Arm 3
Number of subjects	37	24	10
Age, Customized			
Units: Subjects			
< 65 years	31	14	9
>= 65 years	6	10	1
Sex: Female, Male			
Units: Subjects			
Female	14	11	6
Male	23	13	4
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	36	24	10
Black	1	0	0

Reporting group values	Total		
Number of subjects	71		
Age, Customized			
Units: Subjects			
< 65 years	54		
>= 65 years	17		
Sex: Female, Male			
Units: Subjects			
Female	31		
Male	40		
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	70		
Black	1		

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description: Progressive or metastatic bone or soft tissue sarcomas	
Reporting group title	Arm 2
Reporting group description: Progressive gastrointestinal stromal tumors (GIST) after failure of prior imatinib and sunitinib 1st and 2nd line	
Reporting group title	Arm 3
Reporting group description: Progressive or metastatic alveolar soft part sarcoma (ASPS)	

Primary: Best overall response rates by Week 16 (ITT)

End point title	Best overall response rates by Week 16 (ITT)
End point description: The best overall response is the best response recorded from treatment start until disease progression/recurrence (both measurement and confirmation criteria). Best lesion response was defined by (Resist Criteria V1 for target and non-target lesions): Complete Response (CR)=at least two determinations of CR 4 weeks apart before progression, Partial Response (PR)=at least two determinations of CR 4 weeks apart before progression (and not qualifying for a CR), Stable Disease (SD)=at least one SD assessment >6 weeks after start of treatment and Progressive Disease (PD)=Progression or death due to underlying cancer ≤16 weeks after start of treatment. PD without radiologic evidence were classified as progression only, when clear evidence of clinical deterioration was available and patient discontinued due to "disease progression". Unknown (UNK) = all other cases. There were no CR or PR responses.	
End point type	Primary
End point timeframe: Baseline up to 16 weeks	

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	24	10	
Units: percentage of participants				
Stable Disease	41	33	100	
Progressive Disease	51	63	0	
Unknown	8	4	0	

Statistical analyses

Statistical analysis title	ORR analysis
Comparison groups	Arm 1 v Arm 2 v Arm 3

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1
Method	Clopper-Person confidence interval
Parameter estimate	percentage of participants
Point estimate	40.5
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	29.5
upper limit	52.4

Secondary: Objective tumor response rates (Complete Response and Partial Response) at Week 16 (ITT)

End point title	Objective tumor response rates (Complete Response and Partial Response) at Week 16 (ITT)
-----------------	--

End point description:

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Best lesion response was defined by (Resist Criteria V1 for target and non-target lesions).

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to approximately 16 weeks

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	24	10	
Units: percentage of participants				
Complete response	0	0	0	
Partial response	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (CR, PR, SD) at 16 weeks.

End point title	Duration of response (CR, PR, SD) at 16 weeks.
-----------------	--

End point description:

Duration of response (CR, PR or SD) applied only to those patients whose best overall response was CR, PR or SD based on local radiologic assessments and was defined as the time from start of treatment to progression or death from underlying disease. Patients not experiencing progression or death at 16 weeks were censored with the date of their last tumor assessment. Data was rounded up. Duration of response was explored using the Kaplan-Meier method.

End point type	Secondary
End point timeframe:	
Baseline up to 16 weeks	

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	8	10	
Units: percentage of participants	60	63	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) at 16 weeks

End point title	Progression-free survival (PFS) at 16 weeks
End point description:	
Progression-free survival (PFS) was defined as the time from the date of start of treatment to the date of event defined as the first documented progression or death from any cause. If a patient had not had an event, PFS was censored at the date of the last adequate tumor assessment at week 16. Data was rounded.	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	24	10	
Units: percentage of participants	35	31	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) (ITT)

End point title	Time to progression (TTP) (ITT)
End point description:	
Time to progression (TTP) was defined as the time from the date of start of treatment to the date of event defined as the first documented progression or death from underlying disease. If a patient had not had an event, TTP was censored at the date of the last adequate tumor assessment, which was the date of Visit 6 (Week 16) for the core phase and the last available tumor assessment for the follow-up phase. TTP was explored by using the Kaplan-Meier method.	
End point type	Secondary

End point timeframe:
Baseline up to 16 weeks

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	24	10	
Units: days				
median (confidence interval 95%)	57 (55 to 114)	57 (32 to 135)	499 (231 to 704)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at Week 16 (ITT)

End point title	Overall survival (OS) at Week 16 (ITT)
End point description: Overall survival (OS) was defined as the time from the date of start of treatment to death from any cause. If a patient was not known to have died, OS was censored at the date of the last contact, which was the date of Visit 6 (Week 16) for the core phase and the last available visit for the follow-up phase. OS was explored by using the Kaplan-Meier method.	
End point type	Secondary
End point timeframe: Baseline up to 16 weeks	

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	24	10	
Units: percentage of participants	69	57	100	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 16 weeks

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Arm I
-----------------------	-------

Reporting group description:

Arm I

Reporting group title	Arm II
-----------------------	--------

Reporting group description:

Arm II

Reporting group title	Arm III
-----------------------	---------

Reporting group description:

Arm III

Serious adverse events	Arm I	Arm II	Arm III
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 37 (40.54%)	14 / 24 (58.33%)	8 / 10 (80.00%)
number of deaths (all causes)	8	4	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ALVEOLAR SOFT PART SARCOMA METASTATIC			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

CAPILLARY LEAK SYNDROME			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
CHEST PAIN			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISEASE PROGRESSION			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	6 / 37 (16.22%)	5 / 24 (20.83%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 6	1 / 5	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	0 / 10 (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
LOCALISED OEDEMA			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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

PAIN	subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
PYREXIA	subjects affected / exposed	2 / 37 (5.41%)	1 / 24 (4.17%)	1 / 10 (10.00%)
	occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders				
COUGH	subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
DYSPNOEA	subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	0 / 10 (0.00%)
	occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS	subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders				
DELIRIUM	subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
DISORIENTATION	subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
FEAR	subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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

Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
WEIGHT DECREASED			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
Injury, poisoning and procedural complications			
BONE CONTUSION			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JAW FRACTURE			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ATRIAL FLUTTER			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
Nervous system disorders			
COGNITIVE DISORDER			

subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
SCIATICA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
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	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
LYMPHOPENIA			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
PANCYTOPENIA			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 37 (2.70%)	3 / 24 (12.50%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
NAUSEA			

subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBILEUS			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
VOMITING			
subjects affected / exposed	1 / 37 (2.70%)	3 / 24 (12.50%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
JAUNDICE			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
INFECTION			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
PERITONITIS BACTERIAL			

subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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
PNEUMONIA			
subjects affected / exposed	3 / 37 (8.11%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPERINFECTION			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	0 / 10 (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
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
subjects affected / exposed	0 / 37 (0.00%)	2 / 24 (8.33%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOVOLAEMIA			

subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	0 / 10 (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

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

Non-serious adverse events	Arm I	Arm II	Arm III
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 37 (94.59%)	21 / 24 (87.50%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
TUMOUR PAIN			
subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
AORTIC ANEURYSM			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
HAEMATOMA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
LYMPHOEDEMA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 37 (8.11%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences (all)	3	1	1
CHEST PAIN			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
CHILLS			

subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
FATIGUE			
subjects affected / exposed	10 / 37 (27.03%)	9 / 24 (37.50%)	5 / 10 (50.00%)
occurrences (all)	12	9	6
DYSPLASIA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	3 / 37 (8.11%)	1 / 24 (4.17%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
GENERALISED OEDEMA			
subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
IMPAIRED HEALING			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
MEDICAL DEVICE PAIN			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
MUCOSAL INFLAMMATION			
subjects affected / exposed	10 / 37 (27.03%)	4 / 24 (16.67%)	3 / 10 (30.00%)
occurrences (all)	11	4	5
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
OEDEMA PERIPHERAL			
subjects affected / exposed	6 / 37 (16.22%)	6 / 24 (25.00%)	3 / 10 (30.00%)
occurrences (all)	6	7	6
PAIN			
subjects affected / exposed	3 / 37 (8.11%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
PERIPHERAL SWELLING			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1

PYREXIA subjects affected / exposed occurrences (all)	10 / 37 (27.03%) 13	3 / 24 (12.50%) 3	3 / 10 (30.00%) 5
Immune system disorders CONTRAST MEDIA ALLERGY subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 24 (4.17%) 1	2 / 10 (20.00%) 2
Reproductive system and breast disorders AMENORRHOEA subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
VAGINAL DISCHARGE subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
MENORRHAGIA subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 2
VULVOVAGINAL INFLAMMATION subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 4	3 / 24 (12.50%) 3	5 / 10 (50.00%) 9
DRY THROAT subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
DYSPNOEA subjects affected / exposed occurrences (all)	8 / 37 (21.62%) 8	6 / 24 (25.00%) 6	2 / 10 (20.00%) 3
EPISTAXIS subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	4 / 24 (16.67%) 5	1 / 10 (10.00%) 3
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 2

PLEURAL EFFUSION			
subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
PLEURISY			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
PNEUMONITIS			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
INSOMNIA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
SLEEP DISORDER			
subjects affected / exposed	2 / 37 (5.41%)	2 / 24 (8.33%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 37 (10.81%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	3 / 37 (8.11%)	3 / 24 (12.50%)	0 / 10 (0.00%)
occurrences (all)	3	3	0
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
BLOOD CREATININE INCREASED			
subjects affected / exposed	3 / 37 (8.11%)	1 / 24 (4.17%)	0 / 10 (0.00%)
occurrences (all)	3	1	0

BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	4 / 37 (10.81%)	3 / 24 (12.50%)	0 / 10 (0.00%)
occurrences (all)	4	3	0
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	4 / 37 (10.81%)	7 / 24 (29.17%)	1 / 10 (10.00%)
occurrences (all)	4	7	1
CLOSTRIDIUM TEST POSITIVE			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	6 / 37 (16.22%)	3 / 24 (12.50%)	0 / 10 (0.00%)
occurrences (all)	6	3	0
TRANSAMINASES INCREASED			
subjects affected / exposed	5 / 37 (13.51%)	5 / 24 (20.83%)	2 / 10 (20.00%)
occurrences (all)	5	5	3
WEIGHT DECREASED			
subjects affected / exposed	7 / 37 (18.92%)	7 / 24 (29.17%)	1 / 10 (10.00%)
occurrences (all)	7	7	1
Injury, poisoning and procedural complications			
RADIATION SKIN INJURY			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cardiac disorders			
BUNDLE BRANCH BLOCK RIGHT			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CARDIOMEGALY			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
SINUS BRADYCARDIA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
TACHYCARDIA			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1

Nervous system disorders	DYSAESTHESIA			
	subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	1	0	2
	DYSGEUSIA			
	subjects affected / exposed	3 / 37 (8.11%)	4 / 24 (16.67%)	1 / 10 (10.00%)
	occurrences (all)	3	4	1
HEADACHE	subjects affected / exposed	4 / 37 (10.81%)	2 / 24 (8.33%)	5 / 10 (50.00%)
	occurrences (all)	4	2	10
MIGRAINE	subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	1 / 10 (10.00%)
	occurrences (all)	0	1	1
SEIZURE	subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	0	0	1
Blood and lymphatic system disorders				
ANAEMIA	subjects affected / exposed	8 / 37 (21.62%)	9 / 24 (37.50%)	3 / 10 (30.00%)
	occurrences (all)	8	9	4
ANAEMIA OF MALIGNANT DISEASE	subjects affected / exposed	1 / 37 (2.70%)	2 / 24 (8.33%)	0 / 10 (0.00%)
	occurrences (all)	1	2	0
LEUKOPENIA	subjects affected / exposed	3 / 37 (8.11%)	1 / 24 (4.17%)	1 / 10 (10.00%)
	occurrences (all)	4	1	4
LYMPHOPENIA	subjects affected / exposed	1 / 37 (2.70%)	2 / 24 (8.33%)	0 / 10 (0.00%)
	occurrences (all)	1	2	0
THROMBOCYTOPENIA	subjects affected / exposed	5 / 37 (13.51%)	0 / 24 (0.00%)	0 / 10 (0.00%)
	occurrences (all)	7	0	0
Ear and labyrinth disorders				
VERTIGO	subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	2 / 10 (20.00%)
	occurrences (all)	1	0	3
Eye disorders				

LACRIMATION INCREASED			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
MYOPIA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
VISION BLURRED			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	4 / 37 (10.81%)	7 / 24 (29.17%)	3 / 10 (30.00%)
occurrences (all)	4	7	5
APHTHOUS ULCER			
subjects affected / exposed	3 / 37 (8.11%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
ASCITES			
subjects affected / exposed	1 / 37 (2.70%)	4 / 24 (16.67%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
CONSTIPATION			
subjects affected / exposed	1 / 37 (2.70%)	3 / 24 (12.50%)	2 / 10 (20.00%)
occurrences (all)	1	3	2
DIARRHOEA			
subjects affected / exposed	5 / 37 (13.51%)	6 / 24 (25.00%)	3 / 10 (30.00%)
occurrences (all)	5	6	7
DRY MOUTH			
subjects affected / exposed	1 / 37 (2.70%)	3 / 24 (12.50%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
DYSPEPSIA			
subjects affected / exposed	0 / 37 (0.00%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
DYSPHAGIA			

subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
FLATULENCE			
subjects affected / exposed	1 / 37 (2.70%)	3 / 24 (12.50%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
GASTROINTESTINAL DISORDER			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GINGIVAL BLEEDING			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
MOUTH ULCERATION			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
NAUSEA			
subjects affected / exposed	8 / 37 (21.62%)	8 / 24 (33.33%)	3 / 10 (30.00%)
occurrences (all)	9	9	4
PROCTITIS			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
STOMATITIS			
subjects affected / exposed	10 / 37 (27.03%)	4 / 24 (16.67%)	5 / 10 (50.00%)
occurrences (all)	10	4	6
TOOTHACHE			
subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
VOMITING			
subjects affected / exposed	6 / 37 (16.22%)	5 / 24 (20.83%)	3 / 10 (30.00%)
occurrences (all)	6	5	6
Hepatobiliary disorders			
HEPATIC LESION			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
ACNE			

subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
DRY SKIN			
subjects affected / exposed	2 / 37 (5.41%)	2 / 24 (8.33%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
ECZEMA			
subjects affected / exposed	3 / 37 (8.11%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
NAIL DISORDER			
subjects affected / exposed	3 / 37 (8.11%)	0 / 24 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
NIGHT SWEATS			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	2 / 37 (5.41%)	2 / 24 (8.33%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PRURITUS			
subjects affected / exposed	2 / 37 (5.41%)	1 / 24 (4.17%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
RASH			
subjects affected / exposed	8 / 37 (21.62%)	5 / 24 (20.83%)	3 / 10 (30.00%)
occurrences (all)	8	7	4
TELANGIECTASIA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	1 / 37 (2.70%)	2 / 24 (8.33%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
NOCTURIA			

subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 4	3 / 24 (12.50%) 3	0 / 10 (0.00%) 0
DYSURIA subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	1 / 24 (4.17%) 1	1 / 10 (10.00%) 2
URINARY RETENTION subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	2 / 24 (8.33%) 2	0 / 10 (0.00%) 0
Endocrine disorders CUSHING'S SYNDROME subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
HYPERTHYROIDISM subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	1 / 24 (4.17%) 1	1 / 10 (10.00%) 1
TOXIC NODULAR GOITRE subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 2	1 / 24 (4.17%) 1	3 / 10 (30.00%) 4
BACK PAIN subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
MUSCULOSKELETAL DISORDER subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
MUSCULOSKELETAL PAIN subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	0 / 24 (0.00%) 0	3 / 10 (30.00%) 5
MUSCULOSKELETAL STIFFNESS subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 24 (0.00%) 0	1 / 10 (10.00%) 1
PAIN IN EXTREMITY			

subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	2 / 10 (20.00%)
occurrences (all)	2	1	2
PAIN IN JAW			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	4 / 37 (10.81%)	1 / 24 (4.17%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
CHRONIC SINUSITIS			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CYSTITIS			
subjects affected / exposed	1 / 37 (2.70%)	1 / 24 (4.17%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
FEBRILE INFECTION			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GASTROENTERITIS			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
INFLUENZA			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
ORAL INFECTION			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PHARYNGITIS			
subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PNEUMONIA			
subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2

RHINITIS	subjects affected / exposed	1 / 37 (2.70%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	1	0	1
SINUSITIS	subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	0	0	1
URINARY TRACT INFECTION	subjects affected / exposed	3 / 37 (8.11%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	3	0	1
VIRAL UPPER RESPIRATORY TRACT INFECTION	subjects affected / exposed	4 / 37 (10.81%)	1 / 24 (4.17%)	5 / 10 (50.00%)
	occurrences (all)	5	2	15
Metabolism and nutrition disorders				
CACHEXIA	subjects affected / exposed	0 / 37 (0.00%)	2 / 24 (8.33%)	1 / 10 (10.00%)
	occurrences (all)	0	2	1
DECREASED APPETITE	subjects affected / exposed	13 / 37 (35.14%)	6 / 24 (25.00%)	1 / 10 (10.00%)
	occurrences (all)	14	7	2
HYPERGLYCAEMIA	subjects affected / exposed	2 / 37 (5.41%)	0 / 24 (0.00%)	0 / 10 (0.00%)
	occurrences (all)	2	0	0
HYPOCALCAEMIA	subjects affected / exposed	0 / 37 (0.00%)	2 / 24 (8.33%)	0 / 10 (0.00%)
	occurrences (all)	0	2	0
HYPOKALAEMIA	subjects affected / exposed	10 / 37 (27.03%)	5 / 24 (20.83%)	0 / 10 (0.00%)
	occurrences (all)	12	6	0
IRON DEFICIENCY	subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	0	0	1
TYPE 1 DIABETES MELLITUS	subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	0	0	1
TYPE 2 DIABETES MELLITUS				

subjects affected / exposed	0 / 37 (0.00%)	0 / 24 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2008	The original study indication was separated into patients with progressive or metastatic bone and soft tissue sarcoma (except for GIST) and patients with gastrointestinal stromal tumor (GIST) after failure or intolerance of treatment with imatinib or sunitinib in 1st and 2nd line. This new patient population with GIST was to be treated according to the original protocol and to be analyzed separately.
11 August 2009	A third indication arm, focusing on patients with progressive or metastatic alveolar soft part sarcoma (ASPS) was added to the 2 previous arms. Treatment, sample size estimation, and mode of statistical analyses for new this Arm III were the same as for the 2 other arms. All patients with ASPS that were initially included in Arm I of the study were transferred to Arm III for analyses.
22 March 2010	Comprehensive screening procedures for HBV and HCV were amended to the study protocol. • The considerations on CYP3A4 inducers and inhibitors were revised comprehensively and potential interactions with P-glycoprotein (PgP) additionally included.
23 May 2011	Enrolment in Arm III was slow and it was decided to stop enrolment in that arm. However, patients already enrolled into Arm III were to continue treatment and follow-up as foreseen by the protocol. The final analysis of Arm III was to be done once all patients had completed the study or discontinued prematurely. Since the sample size required for the decision algorithm was not reached, data for Arm III were to be summarized descriptively, and results were to be interpreted purely exploratively.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported