Clinical trial results:
A Phase II study of pazopanib (GW786034, NSC# 737754) in children, adolescents, and young adults with refractory solid tumors

Summary

EudraCT number	2013-003595-12
Trial protocol	Outside EU/EEA CZ SK ES HU FR
Global end of trial date	05 November 2019

Results information

Result version number	v2 (current)
This version publication date	03 September 2020
First version publication date	20 May 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	116731

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01956669
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CPZP034X2203

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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000601-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the Investigator-assessed Objective Response Rate (ORR) of pazopanib in children, adolescents, and young adults with relapsed or refractory solid tumors, as defined by the following cohorts: • rhabdomyosarcoma (RMS); • nonrhabdomyosarcomatous soft tissue sarcoma (NRSTS); or • Ewing sarcoma/pPNET (Ewing) Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

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	08 October 2014
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	Canada: 4
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	57
EEA total number of subjects	8

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)	2
Children (2-11 years)	22
Adolescents (12-17 years)	26
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 30 centers in 7 countries: Canada (2), Czech Republic (1), France (1), Hungary (1), Slovakia (1), Spain (1) and USA (23).

Pre-assignment

Screening details:

154 patients were planned to be enrolled in the study. A total of 57 patients were randomized and analyzed: cohort 1 (12), cohort 2 (11), cohort 3 (10), cohort 4 (10), cohort 5 (4), cohort 6 (4) and cohort 7 (6).

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	Cohort 1: rhabdomyosarcoma (RMS)

Arm description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered orally as a tablet at a starting dose of 450 mg/m2/d or as a suspension starting at 225 mg/m2/d. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for the suspension.

Arm title	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)

Arm description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered orally as a tablet at a starting dose of 450 mg/m2/d or as a suspension starting at 225 mg/m2/d. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for the suspension.

Arm title	Cohort 3: Ewing sarcoma/pPNET (Ewing)

Arm description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered orally as a tablet at a starting dose of 450 mg/m2/d or as a suspension starting at 225 mg/m2/d. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for the suspension.

Arm title	Cohort 4 (Osteosarcoma)

Arm description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered orally as a tablet at a starting dose of 450 mg/m2/d or as a suspension starting at 225 mg/m2/d. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for the suspension.

Arm title	Cohort 5: measurable neuroblastoma (mNeuroblastoma)

Arm description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered orally as a tablet at a starting dose of 450 mg/m2/d or as a suspension starting at 225 mg/m2/d. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for the suspension.

Arm title	Cohort 6: evaluable neuroblastoma (eNeuroblastma)

Arm description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6

evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered orally as a tablet at a starting dose of 450 mg/m2/d or as a suspension starting at 225 mg/m2/d. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for the suspension.

Arm title	Cohort 7 (Hepatoblastoma)

Arm description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered orally as a tablet at a starting dose of 450 mg/m2/d or as a suspension starting at 225 mg/m2/d. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for the suspension.

Number of subjects in period 1	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)
Started	12	11	10
PK set	11	11	10
PKES set	4	0	3
Biomarker set	12	11	9
Per Protocol Set (PP set)	9	10	6
Completed	0	0	0
Not completed	12	11	10
Physician decision	-	2	-
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	2	2
Disease Progression	12	7	7

Number of subjects in period 1	Cohort 4 (Osteosarcoma)	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)

Started	10	4	4
PK set	10	4	4
PKES set	0	1	1
Biomarker set	9	3	4
Per Protocol Set (PP set)	9	4	4
Completed	0	0	0
Not completed	10	4	4
Physician decision	-	-	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	-
Disease Progression	8	4	3

Number of subjects in period 1	Cohort 7 (Hepatoblastoma)
Started	6
PK set	6
PKES set	5
Biomarker set	3
Per Protocol Set (PP set)	5
Completed	0
Not completed	6
Physician decision	-
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Disease Progression	5

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: rhabdomyosarcoma (RMS)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 3: Ewing sarcoma/pPNET (Ewing)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 4 (Osteosarcoma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 5: measurable neuroblastoma (mNeuroblastoma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 6: evaluable neuroblastoma (eNeuroblastma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 7 (Hepatoblastoma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)

Number of subjects	12	11	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	8	0	4
Adolescents (12-17 years)	4	10	4
Adults (18-64 years)	0	1	2
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	9.8	15.7	12.6
standard deviation	± 3.82	± 1.19	± 4.67
Sex: Female, Male Units: Participants			
Female	5	4	3
Male	7	7	7
Race/Ethnicity, Customized Units: Subjects			
White/Caucasian/European heritage	9	7	6
African American/African heritage	1	2	3
White Arabic/White North African heritage	0	0	0
American Indian/Alaskan native	0	1	0
Central/South Asian heritage	0	0	1
Japanese heritage	0	0	0
Southeast Asian heritage	0	0	0
Native Hawaiian/other Pacific Islander	0	1	0
Missing	2	0	0

Reporting group values	Cohort 4 (Osteosarcoma)	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)
Number of subjects	10	4	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	2	3	2
Adolescents (12-17 years)	6	0	1
Adults (18-64 years)	2	1	1
From 65-84 years	0	0	0
85 years and over	0	0	0

Age Continuous			
Units: Years			
arithmetic mean	14.1	9.8	13.0
standard deviation	± 3.57	± 5.91	± 4.24
Sex: Female, Male			
Units: Participants			
Female	1	3	3
Male	9	1	1
Race/Ethnicity, Customized			
Units: Subjects			
White/Caucasian/European heritage	7	3	3
African American/African heritage	2	0	1
White Arabic/White North African heritage	0	0	0
American Indian/Alaskan native	0	0	0
Central/South Asian heritage	0	0	0
Japanese heritage	1	0	0
Southeast Asian heritage	0	0	0
Native Hawaiian/other Pacific Islander	0	0	0
Missing	0	1	0

Reporting group values	Cohort 7 (Hepatoblastoma)	Total	
Number of subjects	6	57	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	3	22	
Adolescents (12-17 years)	1	26	
Adults (18-64 years)	0	7	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	5.3		
standard deviation	± 4.80	-	
Sex: Female, Male			
Units: Participants			
Female	5	24	
Male	1	33	
Race/Ethnicity, Customized			
Units: Subjects			
White/Caucasian/European heritage	1	36	
African American/African heritage	1	10	
White Arabic/White North African heritage	2	2	
American Indian/Alaskan native	0	1	
Central/South Asian heritage	0	1	

Japanese heritage	0	1	
Southeast Asian heritage	1	1	
Native Hawaiian/other Pacific Islander	0	1	
Missing	1	4	

End points reporting groups

Reporting group title	Cohort 1: rhabdomyosarcoma (RMS)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 3: Ewing sarcoma/pPNET (Ewing)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 4 (Osteosarcoma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 5: measurable neuroblastoma (mNeuroblastoma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 6: evaluable neuroblastoma (eNeuroblastma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Reporting group title	Cohort 7 (Hepatoblastoma)

Reporting group description:

Subjects were treated with pazopanib GW786034 tablets at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. The maximum daily dose administered was to be 800 mg for the tablet and 400 mg for suspension. If 225 mg/m^2/dose was not tolerated (>=2 DLTs in 6 evaluable subjects), the dose for subjects who required suspension was reduced to 160 mg/m^2/dose. A cycle was defined as 28 days with no rest periods between cycles.

Primary: Percentage of Participants achieving Objective Response Rate (ORR) in subjects' with tumors of primary interest (RMS, NRSTS or Ewing sarcoma/pPNET)

End point title	Percentage of Participants achieving Objective Response Rate (ORR) in subjects' with tumors of primary interest (RMS, NRSTS or Ewing sarcoma/pPNET)[1][2]

End point description:

ORR was defined as the percentage of participants achieving either a Complete Response (CR) or partial Response (PR) based on the Investigator review. The responses were assessed by CT or MRI based on Response Evaluation Criteria In Solid Tumors Criteria (RECIST1.1). CR, disappearance of all target and non-target lesions; PR, at least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment, also no new lesion or progression of any non-target measurable lesion. Confirmation was based on the disease assessment at 1 cycle or at the next scheduled visit after the initial response. Only descriptive analysis performed.

End point type	Primary

End point timeframe:

From date of first dose of study treatment up to 55 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: Only descriptive analysis performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary outcome measure only applies to the three cohorts with tumors of primary scientific interest: rhabdomyosarcoma (RMS), non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS) or Ewing sarcoma/pPNET

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	11	10	
Units: Percentage of Participants				
number (confidence interval 90%)	8.3 (0.4 to 33.9)	0.0 (0.0 to 23.8)	0.0 (0.0 to 25.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants achieving Objective Response Rate (ORR) in subjects' with tumors of secondary interest (Osteosarcoma, mNeuroblastoma, eNeuroblastoma or Hepatoblastoma)

End point title	Percentage of Participants achieving Objective Response Rate (ORR) in subjects' with tumors of secondary interest (Osteosarcoma, mNeuroblastoma, eNeuroblastoma or Hepatoblastoma)[3]

End point description:

ORR was defined as the percentage of participants achieving either a Complete Response (CR) or partial Response (PR) based on the Investigator review. For solid tumors with measurable diseases, such as osteosarcoma, the responses was based on RECIST1.1. CR, disappearance of all target and non target lesions; PR, at least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment, also no new lesion or progression of any non-target measurable lesion. For neuroblastoma with bone marrow response, morphology was determined by hematoxylin and eosin staining of the marrow and aspirates. For neuroblastoma MIBG+ only, the responses was assessed using Curie scale for lesion scoring; For hepatoblastoma, assessment may have included the serum AFP response, in addition to the RECIST1.1

methodology. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to 55 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This secondary outcome measure only applies to the four cohorts with tumors of secondary interest (Osteosarcoma, mNeuroblastoma, eNeuroblastoma or Hepatoblastoma)

End point values	Cohort 4 (Osteosarcoma)	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	4	4	6
Units: Percentage of Participants				
number (confidence interval 90%)	0.0 (0.0 to 25.9)	0.0 (0.0 to 52.7)	0.0 (0.0 to 52.7)	0.0 (0.0 to 39.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as assessed by the Investigator by cohort

End point title	Progression Free Survival (PFS) as assessed by the Investigator by cohort

End point description:

PFS was defined as the interval between the date of first dose of study medication and the earliest date of disease progression or death due to any cause. Disease progression was based on radiographic evidence, and assessments made by the investigator. According to RECIST1.1, disease progression was defined as at least a 20% increase in the sum of the disease measurements for measurable lesions, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions. For participants who did not progress or die, PFS was censored at the date of last adequate assessment or date of last adequate assessment prior to initiation of new anti-cancer therapy. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to 59 months

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	10	10
Units: Months				
median (confidence interval 90%)	1.8 (1.0 to 1.8)	1.8 (0.3 to 13.8)	2.3 (0.2 to 13.5)	1.9 (0.5 to 5.3)

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	6	
Units: Months				
median (confidence interval 90%)	4.9 (0.8 to 6.4)	5.4 (3.6 to 24.4)	1.8 (0.5 to 1.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) by cohort

End point title	Time to progression (TTP) by cohort

End point description:

The TTP was defined as the interval between the date of first dose of protocol therapy and the earliest date of disease progression or death due to disease under study. Subjects were considered to have progressive disease if they had documented progression based on radiologic assessment as determined by investigator review. According to RECIST1.1, disease progression was defined as at least a 20% increase in the sum of the disease measurements for measurable lesions, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to 59 months

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	10	10
Units: Months				
median (confidence interval 90%)	1.8 (1.0 to 1.8)	1.8 (0.3 to 13.8)	2.3 (0.2 to 13.5)	1.9 (0.5 to 5.3)

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	

Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	6	
Units: Months				
median (confidence interval 90%)	4.9 (0.8 to 6.4)	14.9 (5.4 to 24.4)	1.8 (0.5 to 1.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants achieving Clinical Benefit Rate (CBR) by cohort

End point title	Percentage of Participants achieving Clinical Benefit Rate (CBR) by cohort

End point description:

CBR was defined as the percentage of participants achieving either a confirmed complete response (CR) or confirmed partial response (PR) or Stable Disease (SD) for at least two protocol scheduled disease assessments based on RECIST1.1. CR, disappearance of all target and non-target lesions; PR, at least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment, also no new lesion or progression of any non-target measurable lesion; SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to 55 months

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	10	10
Units: Percentage of Participants				
number (confidence interval 90%)	8.3 (0.4 to 33.9)	27.3 (7.9 to 56.4)	20.0 (3.7 to 50.7)	20.0 (3.7 to 50.7)

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	6	
Units: Percentage of Participants				
number (confidence interval 90%)	50.0 (9.8 to 90.2)	25.0 (1.3 to 75.1)	0.0 (0.0 to 39.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by cohort

End point title	Duration of Response (DOR) by cohort

End point description:

DoR was defined as the time from initial response to the first documented disease progression or death due to any cause, and was determined only for those participants from the mITT population with a confirmed response (CR or PR). Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to 59 months

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	10	10
Units: Months				
median (confidence interval 90%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	6	
Units: Months				
median (confidence interval 90%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) by cohort

End point title	Overall Survival (OS) by cohort

End point description:

OS was defined as the time from the first dose of the study medication until death due to any cause. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to 61 months

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	10	10
Units: Months				
median (confidence interval 90%)	5.6 (2.2 to 14.2)	14.6 (1.5 to 20.1)	999 (4.3 to 999)	5.5 (1.5 to 7.0)

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	6	
Units: Months				
median (confidence interval 90%)	999 (2.6 to 999)	5.4 (3.6 to 24.4)	5.7 (0.6 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the plasma concentration-time Curve calculated from time 0 to 8 h postdose (AUC0-8h) and calculated to the last quantifiable concentration point (AUClast) of pazopanib by cohort

End point title	Area Under the plasma concentration-time Curve calculated from time 0 to 8 h postdose (AUC0-8h) and calculated to the last quantifiable concentration point (AUClast) of pazopanib by cohort[4]

End point description:

AUC0-8h and AUClast were calculated using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) and the LLOQ was 0.100 µg/mL. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (0, 0.5, 1, 2, 4, 6 and 8 hours post-dose); Cycle 1 Day 15 ± 1 day (0, 0.5, 1, 2, 4, 6 and 8 hours post-dose)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This secondary outcome measure only applies to: Cohort 1: rhabdomyosarcoma (RMS), Cohort 3: Ewing sarcoma/pPNET (Ewing), Cohort 5: measurable neuroblastoma (mNeuroblastoma), Cohort 6: evaluable neuroblastoma (eNeuroblastma) and Cohort 7 (Hepatoblastoma)

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	1	1
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUC0-8h (C1D1)	195 (± 19.0)	214 (± 93.2)	999 (± 999)	999 (± 999)
AUC0-8h (C1D15)	388 (± 55.9)	266 (± 36.1)	475 (± 999)	566 (± 999)
AUClast (C1D1)	194 (± 19.6)	189 (± 65.8)	999 (± 999)	999 (± 999)
AUClast (C1D15)	966 (± 58.1)	633 (± 35.4)	1230 (± 999)	1490 (± 999)

End point values	Cohort 7 (Hepatoblastoma)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUC0-8h (C1D1)	135 (± 60.2)			
AUC0-8h (C1D15)	229 (± 89.5)			
AUClast (C1D1)	135 (± 60.2)			
AUClast (C1D15)	607 (± 85.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum plasma concentration (Cmax) of pazopanib by cohort

End point title	Observed maximum plasma concentration (Cmax) of pazopanib by cohort[5]

End point description:

Cmax was calculated using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) and the LLOQ was 0.100 µg/mL. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (0, 0.5, 1, 2, 4, 6 and 8 hours post-dose); Cycle 1 Day 15 ± 1 day (0, 0.5, 1, 2, 4, 6 and 8 hours post-dose)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This secondary outcome measure only applies to: Cohort 1: rhabdomyosarcoma (RMS), Cohort 3: Ewing sarcoma/pPNET (Ewing), Cohort 5: measurable neuroblastoma (mNeuroblastoma), Cohort 6: evaluable neuroblastoma (eNeuroblastma) and Cohort 7 (Hepatoblastoma)

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	1	1
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax (C1D1)	34.7 (± 14.7)	35.6 (± 75.9)	0.0 (± 999)	999 (± 999)
Cmax (C1D15)	56.7 (± 53.3)	42.0 (± 42.3)	69.6 (± 999)	80.2 (± 999)

End point values	Cohort 7 (Hepatoblastoma)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax (C1D1)	22.4 (± 73.7)			
Cmax (C1D15)	33.4 (± 95.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach peak or maximum concentration (Tmax) of pazopanib by cohort

End point title	Time to reach peak or maximum concentration (Tmax) of pazopanib by cohort[6]

End point description:

Tmax was calculated using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) and the LLOQ was 0.100 µg/mL. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (0, 0.5, 1, 2, 4, 6 and 8 hours post-dose); Cycle 1 Day 15 ± 1 day (0, 0.5, 1, 2, 4, 6 and 8 hours post-dose)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This secondary outcome measure only applies to: Cohort 1: rhabdomyosarcoma (RMS), Cohort 3: Ewing sarcoma/pPNET (Ewing), Cohort 5: measurable neuroblastoma (mNeuroblastoma), Cohort 6: evaluable neuroblastoma (eNeuroblastma) and Cohort 7 (Hepatoblastoma)

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	1	1
Units: Hours				
median (full range (min-max))				
Tmax (C1D1)	1 (0.00 to 2.00)	2.02 (1.00 to 5.97)	0.00 (0.00 to 0.00)	999 (999 to 999)
Tmax (C1D15)	2.50 (2.00 to 3.03)	1.00 (1.00 to 1.00)	3.47 (3.47 to 3.47)	3.03 (3.03 to 3.03)

End point values	Cohort 7 (Hepatoblastoma)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Hours				
median (full range (min-max))				
Tmax (C1D1)	2.00 (0.00 to 6.00)			
Tmax (C1D15)	3.00 (0.98 to 4.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pazopanib steady-state trough (Ctrough) levels for participants with drug-related grade 2 and above hypertension

End point title	Pazopanib steady-state trough (Ctrough) levels for participants with drug-related grade 2 and above hypertension

End point description:

The relationship between toxicity (including hypertension) and pharmacokinetic parameters (pazopanib trough concentration) was analyzed. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment up to 61 months

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[7]	1	2	1
Units: ng/mL				

geometric mean (geometric coefficient of variation)	()	97.1 (± 999)	35.7 (± 22.6)	35.7 (± 999)

Notes:

[7] - No participants with drug-related grade 2 and above hypertension

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	1	0[8]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	38.0 (± 20.8)	63.7 (± 999)	()	

Notes:

[8] - No participants with drug-related grade 2 and above hypertension

Statistical analyses

No statistical analyses for this end point

Secondary: Summary for Plasma biomarkers levels on Cycle 1 Day 1 and Cycle 2 Day 1 by cohort

End point title	Summary for Plasma biomarkers levels on Cycle 1 Day 1 and Cycle 2 Day 1 by cohort

End point description:

The following biomarker parameters were analyzed: proto-oncogene c-KIT (c-KIT), Fibroblast growth factor (FGF), Placental growth factor PGF), Angiopoietin-1 receptor (TIE2), Vascular endothelial growth factor A (VEGF-A), Vascular endothelial growth factor C (VEGF-C), Vascular endothelial growth factor D (VEGF-D), Vascular endothelial growth factor receptor 1 (VEGFR-1) and Vascular endothelial growth factor receptor 2 (VEGFR-2)). Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

predose Cycle 1 Day 1, Cycle 2 Day 1

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	9	9
Units: picogram/milliliter (pg/mL)				
geometric mean (geometric coefficient of variation)				
c-KIT (C1D1)	139522.4 (± 29.4)	142526.9 (± 24.3)	135024.5 (± 25.9)	137317.7 (± 23.9)
c-KIT (C2D1)	110154.0 (± 14.1)	99962.7 (± 8.2)	94307.1 (± 15.1)	99989.6 (± 18.9)
FGF (C1D1)	7.8 (± 63.1)	6.9 (± 71.1)	8.3 (± 59.1)	5.9 (± 6.0)
FGF (C2D1)	15.1 (± 68.9)	6.2 (± 999)	5.1 (± 999)	999 (± 999)
PGF (C1D1)	19.6 (± 245.7)	8.9 (± 27.6)	9.4 (± 36.9)	10.5 (± 37.0)

PGF (C2D1)	54.6 (± 259.4)	27.8 (± 74.9)	37.4 (± 82.9)	63.2 (± 113.8)
TIE2 (C1D1)	8086.8 (± 26.5)	8180.0 (± 25.0)	7280.6 (± 15.6)	8574.9 (± 7.7)
TIE2 (C2D1)	8340.1 (± 11.5)	7788.8 (± 11.5)	7650.6 (± 22.7)	7894.1 (± 17.4)
VEGF-A (C1D1)	63.8 (± 133.8)	46.1 (± 66.1)	74.0 (± 98.0)	82.9 (± 62.0)
VEGF-A (C2D1)	123.3 (± 140.6)	77.2 (± 166.8)	171.8 (± 126.0)	179.4 (± 98.7)
VEGF-C (C1D1)	121.4 (± 1.6)	152.6 (± 84.7)	999 (± 999)	999 (± 999)
VEGF-C (C2D1)	105.9 (± 999)	339.9 (± 999)	999 (± 999)	999 (± 999)
VEGF-D (C1D1)	354.2 (± 54.6)	372.3 (± 20.5)	394.6 (± 21.6)	375.4 (± 43.9)
VEGF-D (C2D1)	434.6 (± 77.4)	501.8 (± 43.0)	448.6 (± 16.9)	551.7 (± 14.4)
VEGFR-1 (C1D1)	394.5 (± 292.3)	175.7 (± 174.4)	224.4 (± 121.7)	134.6 (± 113.7)
VEGFR-1 (C2D1)	87.5 (± 98.5)	534.3 (± 709.9)	93.8 (± 121.1)	140.0 (± 231.3)
VEGFR-2 (C1D1)	31451.9 (± 22.6)	31745.8 (± 20.6)	33724.8 (± 15.8)	34993.1 (± 17.6)
VEGFR-2 (C2D1)	25099.6 (± 22.9)	23059.9 (± 21.6)	23502.8 (± 1.0)	22154.3 (± 15.1)

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	4	3	
Units: picogram/milliliter (pg/mL)				
geometric mean (geometric coefficient of variation)				
c-KIT (C1D1)	142630.1 (± 18.0)	113596.9 (± 26.6)	119921.9 (± 30.6)	
c-KIT (C2D1)	121497.7 (± 23.0)	71216.5 (± 2.0)	154558.2 (± 999)	
FGF (C1D1)	999 (± 999)	13.5 (± 999)	999 (± 999)	
FGF (C2D1)	6.6 (± 999)	999 (± 999)	999 (± 999)	
PGF (C1D1)	9.3 (± 6.2)	13.7 (± 126.6)	8.6 (± 29.7)	
PGF (C2D1)	30.3 (± 300.5)	225.2 (± 840.1)	39.4 (± 999)	
TIE2 (C1D1)	7439.8 (± 4.6)	8179.2 (± 30.0)	7842.2 (± 18.3)	
TIE2 (C2D1)	8026.6 (± 28.2)	6824.4 (± 32.0)	8540.0 (± 999)	
VEGF-A (C1D1)	48.8 (± 39.0)	62.2 (± 268.3)	129.3 (± 46.6)	
VEGF-A (C2D1)	219.3 (± 40.4)	1057.5 (± 750.0)	208.9 (± 999)	
VEGF-C (C1D1)	999 (± 999)	999 (± 999)	999 (± 999)	
VEGF-C (C2D1)	999 (± 999)	999 (± 999)	999 (± 999)	
VEGF-D (C1D1)	645.4 (± 108.7)	351.7 (± 12.1)	370.0 (± 75.9)	
VEGF-D (C2D1)	501.4 (± 50.1)	791.4 (± 51.1)	400.4 (± 999)	
VEGFR-1 (C1D1)	95.8 (± 42.9)	367.5 (± 130.8)	173.4 (± 109.6)	
VEGFR-1 (C2D1)	69.4 (± 4.9)	76.4 (± 14.6)	1811.6 (± 999)	

VEGFR-2 (C1D1)	31682.1 (± 12.1)	39342.8 (± 14.7)	30780.5 (± 6.0)	
VEGFR-2 (C2D1)	25385.9 (± 42.9)	13621.6 (± 68.5)	26266.9 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary for Change from Baseline levels of Plasma biomarkers by high and low Pazopanib steady state trough concentration and cohort

End point title	Summary for Change from Baseline levels of Plasma biomarkers by high and low Pazopanib steady state trough concentration and cohort

End point description:

Participants with steady state trough concentration median levels for the following biomarker parameters (proto-oncogene c-KIT (c-KIT), Fibroblast growth factor (FGF), Placental growth factor PGF), Angiopoietin-1 receptor (TIE2), Vascular endothelial growth factor A (VEGF-A), Vascular endothelial growth factor C (VEGF-C), Vascular endothelial growth factor D (VEGF-D), Vascular endothelial growth factor receptor 1 (VEGFR-1) and Vascular endothelial growth factor receptor 2 (VEGFR-2)) above the median levels were classified as high or below median levels were classified as low. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

predose Cycle 1 Day 1, Cycle 2 Day 1

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	9	9
Units: picogram/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
c-KIT high trough concentration	999 (± 999)	999 (± 999)	-76081.1 (± 999)	-40512.6 (± 999)
c-KIT low trough concentration	-13480.5 (± 999)	-44973.7 (± 999)	999 (± 999)	-48764.1 (± 999)
FGF high trough concentration	999 (± 999)	999 (± 999)	-7.0 (± 999)	999 (± 999)
FGF low trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
PGF high trough concentration	999 (± 999)	999 (± 999)	78.3 (± 999)	15.6 (± 999)
PGF low trough concentration	999 (± 999)	5.6 (± 999)	999 (± 999)	28.3 (± 999)
TIE2 high trough concentration	999 (± 999)	999 (± 999)	2553.0 (± 999)	-509.4 (± 999)
TIE2 low trough concentration	1212.4 (± 999)	-1514.9 (± 999)	999 (± 999)	-918.4 (± 999)
VEGF-A high trough concentration	999 (± 999)	999 (± 999)	358.8 (± 999)	34.3 (± 999)
VEGF-A low trough concentration	2436.6 (± 999)	18.5 (± 999)	999 (± 999)	52.3 (± 999)
VEGF-C high trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
VEGF-C low trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
VEGF-D high trough concentration	999 (± 999)	999 (± 999)	88.0 (± 999)	139.7 (± 999)
VEGF-D low trough concentration	423.2 (± 999)	44.1 (± 999)	999 (± 999)	153.5 (± 999)

VEGFR-1 high trough concentration	999 (± 999)	999 (± 999)	-217.5 (± 999)	955.6 (± 999)
VEGFR-1 low trough concentration	484.1 (± 999)	-67.2 (± 999)	999 (± 999)	-7.7 (± 999)
VEGFR-2 high trough concentration	999 (± 999)	999 (± 999)	-2620.0 (± 999)	-16136.9 (± 999)
VEGFR-2 low trough concentration	-12130.8 (± 999)	-7795.4 (± 999)	999 (± 999)	-8588.1 (± 999)

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	4	3	
Units: picogram/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
c-KIT high trough concentration	999 (± 999)	-51199.4 (± 999)	999 (± 999)	
c-KIT low trough concentration	999 (± 999)	-35678.6 (± 999)	999 (± 999)	
FGF high trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	
FGF low trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	
PGF high trough concentration	999 (± 999)	45.4 (± 999)	999 (± 999)	
PGF low trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	
TIE2 high trough concentration	999 (± 999)	-2708.2 (± 999)	999 (± 999)	
TIE2 low trough concentration	999 (± 999)	-473.0 (± 999)	999 (± 999)	
VEGF-A high trough concentration	999 (± 999)	-73.3 (± 999)	999 (± 999)	
VEGF-A low trough concentration	999 (± 999)	39.7 (± 999)	999 (± 999)	
VEGF-C high trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	
VEGF-C low trough concentration	999 (± 999)	999 (± 999)	999 (± 999)	
VEGF-D high trough concentration	999 (± 999)	187.5 (± 999)	999 (± 999)	
VEGF-D low trough concentration	999 (± 999)	90.8 (± 999)	999 (± 999)	
VEGFR-1 high trough concentration	999 (± 999)	-49.7 (± 999)	999 (± 999)	
VEGFR-1 low trough concentration	999 (± 999)	-741.3 (± 999)	999 (± 999)	
VEGFR-2 high trough concentration	999 (± 999)	-16838.7 (± 999)	999 (± 999)	
VEGFR-2 low trough concentration	999 (± 999)	-10529.6 (± 999)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with genetic alterations by low and high values of VEGFA and VEGFR1

End point title	Number of Participants with genetic alterations by low and high values of VEGFA and VEGFR1

End point description:

The frequency of genetic alterations observed in participants was presented by high and low baseline plasma levels for Vascular endothelial growth factor A (VEGF-A) and Vascular endothelial growth factor

receptor 1 (VEGFR-1) biomarkers. The VEGFA and VEGFR1 levels above the median were classified as high and participants with median levels or below were classified as low. Only descriptive analysis performed for participants presenting with a genetic alteration.

End point type	Secondary

End point timeframe:

predose Cycle 1 Day 1, Cycle 2 Day 1

End point values	Cohort 1: rhabdomyosarcoma (RMS)	Cohort 2: non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS)	Cohort 3: Ewing sarcoma/pPNET (Ewing)	Cohort 4 (Osteosarcoma)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[9]	0[10]	0[11]	0[12]
Units: Participants				
VEGFA Low|VHL				
VEGFA High|VHL				
VEGFR1 Low|VHL				
VEGFR1 High|VHL				
VEGFA Low|FLT1				
VEGFA High|FLT1				
VEGFR1 Low|FLT1				
VEGFR1 High|FLT1				
VEGFA Low|KDR				
VEGFA High|KDR				
VEGFR1 Low|KDR				
VEGFR1 High|KDR				
VEGFA Low|HIF1A				
VEGFA High|HIF1A				
VEGFR1 Low|HIF1A				
VEGFR1 High|HIF1A				
VEGFA Low|KRAS				
VEGFA High|KRAS				
VEGFR1 Low|KRAS				
VEGFR1 High|KRAS				
VEGFA Low|PIK3R1				
VEGFA High|PIK3R1				
VEGFR1 Low|PIK3R1				
VEGFR1 High|PIK3R1				
VEGFA Low|MAPK1				
VEGFA High|MAPK1				
VEGFR1 Low|MAPK1				
VEGFR1 High|MAPK1				
VEGFA Low|PLCG1				
VEGFA High|PLCG1				
VEGFR1 Low|PLCG1				
VEGFR1 High|PLCG1				

Notes:

[9] - No Participants with genetic alterations by low and high values of VEGFA and VEGFR1

[10] - No Participants with genetic alterations by low and high values of VEGFA and VEGFR1

[11] - No Participants with genetic alterations by low and high values of VEGFA and VEGFR1

[12] - No Participants with genetic alterations by low and high values of VEGFA and VEGFR1

End point values	Cohort 5: measurable neuroblastoma (mNeuroblastoma)	Cohort 6: evaluable neuroblastoma (eNeuroblastma)	Cohort 7 (Hepatoblastoma)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	1	0[14]	
Units: Participants				
VEGFA Low|VHL		0		
VEGFA High|VHL		0		
VEGFR1 Low|VHL		0		
VEGFR1 High|VHL		0		
VEGFA Low|FLT1		1		
VEGFA High|FLT1		0		
VEGFR1 Low|FLT1		0		
VEGFR1 High|FLT1		1		
VEGFA Low|KDR		0		
VEGFA High|KDR		0		
VEGFR1 Low|KDR		0		
VEGFR1 High|KDR		0		
VEGFA Low|HIF1A		0		
VEGFA High|HIF1A		0		
VEGFR1 Low|HIF1A		0		
VEGFR1 High|HIF1A		0		
VEGFA Low|KRAS		0		
VEGFA High|KRAS		0		
VEGFR1 Low|KRAS		0		
VEGFR1 High|KRAS		0		
VEGFA Low|PIK3R1		0		
VEGFA High|PIK3R1		0		
VEGFR1 Low|PIK3R1		0		
VEGFR1 High|PIK3R1		0		
VEGFA Low|MAPK1		0		
VEGFA High|MAPK1		0		
VEGFR1 Low|MAPK1		0		
VEGFR1 High|MAPK1		0		
VEGFA Low|PLCG1		0		
VEGFA High|PLCG1		0		
VEGFR1 Low|PLCG1		0		
VEGFR1 High|PLCG1		0		

Notes:

[13] - No Participants with genetic alterations by low and high values of VEGFA and VEGFR1

[14] - No Participants with genetic alterations by low and high values of VEGFA and VEGFR1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

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	22.0

Reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Cohort 1	
Reporting group title	Cohort 2
Reporting group description:	
Cohort 2	
Reporting group title	Cohort 3
Reporting group description:	
Cohort 3	
Reporting group title	Cohort 4
Reporting group description:	
Cohort 4	
Reporting group title	Cohort 5
Reporting group description:	
Cohort 5	
Reporting group title	Cohort 6
Reporting group description:	
Cohort 6	
Reporting group title	Cohort 7
Reporting group description:	
Cohort 7	
Reporting group title	All subjects
Reporting group description:	
All subjects	

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	5 / 11 (45.45%)	3 / 10 (30.00%)
number of deaths (all causes)	3	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			

Blood creatinine increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	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
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	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
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	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
Rectal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (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
Pneumothorax			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	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
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (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
Skin infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	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

Serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
number of deaths (all causes)	3	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Left ventricular dysfunction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Intracranial pressure increased			

subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (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
Pneumothorax			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (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
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (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
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 7	All subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	17 / 57 (29.82%)	
number of deaths (all causes)	1	9	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular dysfunction			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
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			
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	11 / 11 (100.00%)	10 / 10 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	2 / 10 (20.00%)
occurrences (all)	1	2	2
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	4 / 12 (33.33%)	3 / 11 (27.27%)	4 / 10 (40.00%)
occurrences (all)	4	3	6
Feeling jittery			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nodule			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 12 (0.00%)	3 / 11 (27.27%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Peripheral swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	5 / 12 (41.67%)	1 / 11 (9.09%)	2 / 10 (20.00%)
occurrences (all)	5	1	3
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Genital pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vulvovaginal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Catarrh			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	3 / 12 (25.00%)	2 / 11 (18.18%)	3 / 10 (30.00%)
occurrences (all)	5	2	3
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Epistaxis			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Haemoptysis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			

subjects affected / exposed	3 / 12 (25.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	3	0	2
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	2
Sinus pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Intentional self-injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Irritability			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	3 / 12 (25.00%)	0 / 11 (0.00%)	3 / 10 (30.00%)
occurrences (all)	3	0	3
Amylase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 12 (33.33%)	0 / 11 (0.00%)	3 / 10 (30.00%)
occurrences (all)	7	0	3
Blood alkaline phosphatase			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 11 (27.27%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Blood urea increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Carbon dioxide decreased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Cardiac murmur			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Creatinine urine increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemoglobin increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Lymphocyte count decreased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Lymphocyte count increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Monocyte count increased			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	2 / 12 (16.67%)	2 / 11 (18.18%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Platelet count decreased			
subjects affected / exposed	4 / 12 (33.33%)	1 / 11 (9.09%)	2 / 10 (20.00%)
occurrences (all)	5	1	3
Protein total increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Red blood cell count decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vanillyl mandelic acid urine increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
White blood cell count decreased			
subjects affected / exposed	3 / 12 (25.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	5	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrostomy tube site complication			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tongue injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Wound complication			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Dysgeusia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	2 / 12 (16.67%)	3 / 11 (27.27%)	2 / 10 (20.00%)
occurrences (all)	2	4	2
Hypersomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Leukopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Deafness bilateral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Erythema of eyelid			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Eye pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eyelash discolouration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	5 / 12 (41.67%)	4 / 11 (36.36%)	1 / 10 (10.00%)
occurrences (all)	6	5	1
Abdominal pain upper			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Cheilitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)	3 / 11 (27.27%)	4 / 10 (40.00%)
occurrences (all)	6	4	5
Dyspepsia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Flatulence			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	4 / 12 (33.33%)	1 / 11 (9.09%)	5 / 10 (50.00%)
occurrences (all)	4	1	6
Oral dysaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Toothache			

subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	8 / 12 (66.67%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	15	0	3
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hair colour changes			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	3 / 10 (30.00%)
occurrences (all)	1	2	3
Hyperhidrosis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Macule			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nail disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Rash macular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Skin depigmentation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin erosion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin hypopigmentation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Skin lesion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Chromaturia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	2 / 12 (16.67%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
Haemoglobinuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Leukocyturia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	4 / 12 (33.33%)	1 / 11 (9.09%)	2 / 10 (20.00%)
occurrences (all)	4	1	3
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 12 (16.67%)	2 / 11 (18.18%)	3 / 10 (30.00%)
occurrences (all)	2	2	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	1	1

Back pain			
subjects affected / exposed	2 / 12 (16.67%)	4 / 11 (36.36%)	5 / 10 (50.00%)
occurrences (all)	3	4	5
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Groin pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Joint effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Neck pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	3 / 12 (25.00%)	2 / 11 (18.18%)	2 / 10 (20.00%)
occurrences (all)	7	2	2
Trismus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Folliculitis			

subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 12 (25.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 12 (33.33%)	4 / 11 (36.36%)	4 / 10 (40.00%)
occurrences (all)	4	5	4
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	0	1	1

Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	1 / 10 (10.00%)
occurrences (all)	1	2	2
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Hypophosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Vitamin D deficiency			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hot flush			

subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	4 / 10 (40.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	4	1	1
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	2	0	2
Feeling jittery			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Nodule			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Pain			

subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Peripheral swelling			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Genital pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Catarrh			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	3 / 10 (30.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	1
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Epistaxis			

subjects affected / exposed	2 / 10 (20.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	2	1	2
Haemoptysis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Hiccups			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Pneumothorax			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Sinus pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sneezing			

subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Depression			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Intentional self-injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 10 (40.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	0	2
Amylase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 10 (30.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	4	3	1
Blood alkaline phosphatase			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Carbon dioxide decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Creatinine urine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ejection fraction decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haemoglobin increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Lymphocyte count increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Monocyte count increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Platelet count decreased			
subjects affected / exposed	5 / 10 (50.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	7	1	1
Protein total increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vanillyl mandelic acid urine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	2
White blood cell count decreased			
subjects affected / exposed	5 / 10 (50.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	7	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Fall			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrostomy tube site complication			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tongue injury			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Wound complication			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Supraventricular extrasystoles			

subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	3 / 10 (30.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	1
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 10 (20.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Hypersomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	3 / 10 (30.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	3	3	2
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Lymphopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Deafness bilateral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Erythema of eyelid			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye pruritus			

subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eyelash discolouration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	4 / 10 (40.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	4	2	1
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	1
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	2	3	5
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	3 / 10 (30.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	4	4	3
Oral dysaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Oral pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 10 (30.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	5	3	4
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dermatitis acneiform			

subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hair colour changes			
subjects affected / exposed	2 / 10 (20.00%)	1 / 4 (25.00%)	3 / 4 (75.00%)
occurrences (all)	2	1	3
Hyperhidrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Macule			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Skin depigmentation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin erosion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin hypopigmentation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Chromaturia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Haematuria			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Haemoglobinuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Leukocyturia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Micturition urgency			

subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	3 / 10 (30.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	2	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Back pain			
subjects affected / exposed	2 / 10 (20.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Bone pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Groin pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Joint effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Myalgia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	4 / 10 (40.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	6	1	1
Trismus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Folliculitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 10 (40.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	4	1	2
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hyponatraemia			

subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	2
Hypophosphataemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 7	All subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	57 / 57 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)	13 / 57 (22.81%)	
occurrences (all)	2	13	
Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	17 / 57 (29.82%)	
occurrences (all)	4	21	
Feeling jittery			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Gait disturbance			

subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Nodule			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	4	
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	0 / 6 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	4	
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	4 / 6 (66.67%)	16 / 57 (28.07%)	
occurrences (all)	7	20	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Genital pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Vulvovaginal pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	2 / 6 (33.33%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Catarrh			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 6 (16.67%)	13 / 57 (22.81%)	
occurrences (all)	1	15	
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	6 / 57 (10.53%)	
occurrences (all)	0	6	
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	7 / 57 (12.28%)	
occurrences (all)	0	8	
Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
Hiccups			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	4	
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	8 / 57 (14.04%)	
occurrences (all)	0	8	
Pleural effusion			

subjects affected / exposed	1 / 6 (16.67%)	3 / 57 (5.26%)	
occurrences (all)	1	4	
Pneumothorax			
subjects affected / exposed	1 / 6 (16.67%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Rhinitis allergic			
subjects affected / exposed	1 / 6 (16.67%)	3 / 57 (5.26%)	
occurrences (all)	1	3	
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	5 / 57 (8.77%)	
occurrences (all)	0	7	
Sinus pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	3 / 57 (5.26%)	
occurrences (all)	1	3	
Depression			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Intentional self-injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	

Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 6 (16.67%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	14 / 57 (24.56%)	
occurrences (all)	4	16	
Amylase increased			
subjects affected / exposed	1 / 6 (16.67%)	3 / 57 (5.26%)	
occurrences (all)	1	4	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 6 (66.67%)	16 / 57 (28.07%)	
occurrences (all)	4	22	
Blood alkaline phosphatase			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 57 (3.51%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	4 / 57 (7.02%)	
occurrences (all)	1	4	
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Blood urea increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Carbon dioxide decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	3	
Cardiac murmur			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Creatinine urine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	4	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	4 / 57 (7.02%)	
occurrences (all)	3	4	
Haemoglobin increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	5	
Lymphocyte count decreased			
subjects affected / exposed	1 / 6 (16.67%)	5 / 57 (8.77%)	
occurrences (all)	1	5	
Lymphocyte count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Monocyte count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Neutrophil count decreased			

subjects affected / exposed	2 / 6 (33.33%)	10 / 57 (17.54%)	
occurrences (all)	2	11	
Platelet count decreased			
subjects affected / exposed	2 / 6 (33.33%)	16 / 57 (28.07%)	
occurrences (all)	2	20	
Protein total increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Red blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Urine analysis abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Vanillyl mandelic acid urine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	2 / 6 (33.33%)	7 / 57 (12.28%)	
occurrences (all)	3	9	
White blood cell count decreased			
subjects affected / exposed	3 / 6 (50.00%)	13 / 57 (22.81%)	
occurrences (all)	3	17	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	5 / 57 (8.77%)	
occurrences (all)	0	5	
Fall			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Gastrostomy tube site complication			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Procedural pain			

subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Tongue injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Wound complication			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 57 (5.26%)	
occurrences (all)	2	4	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	6 / 57 (10.53%)	
occurrences (all)	0	6	
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Headache			

subjects affected / exposed	1 / 6 (16.67%)	11 / 57 (19.30%)	
occurrences (all)	6	17	
Hypersomnia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Lethargy			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 57 (3.51%)	
occurrences (all)	2	3	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 6 (33.33%)	12 / 57 (21.05%)	
occurrences (all)	3	15	
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	6 / 57 (10.53%)	
occurrences (all)	0	8	
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Cerumen impaction			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Deafness bilateral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Erythema of eyelid			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Eye pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Eyelash discolouration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	19 / 57 (33.33%)	
occurrences (all)	2	21	
Abdominal pain upper			

subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	8 / 57 (14.04%)	
occurrences (all)	2	9	
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	17 / 57 (29.82%)	
occurrences (all)	1	26	
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	20 / 57 (35.09%)	
occurrences (all)	3	25	
Oral dysaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
Toothache			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	4 / 6 (66.67%)	20 / 57 (35.09%)	
occurrences (all)	9	39	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Dermatitis contact			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hair colour changes			
subjects affected / exposed	1 / 6 (16.67%)	13 / 57 (22.81%)	
occurrences (all)	1	13	
Hyperhidrosis			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Macule				
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Nail disorder				
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Pruritus				
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)		
occurrences (all)	0	3		
Rash macular				
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Rash maculo-papular				
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)		
occurrences (all)	0	2		
Skin depigmentation				
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Skin erosion				
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Skin hypopigmentation				
subjects affected / exposed	0 / 6 (0.00%)	3 / 57 (5.26%)		
occurrences (all)	0	3		
Skin lesion				
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Urticaria				
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)		
occurrences (all)	0	2		

Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Chromaturia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	7 / 57 (12.28%)	
occurrences (all)	0	7	
Haemoglobinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Leukocyturia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Micturition urgency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	1 / 6 (16.67%)	13 / 57 (22.81%)	
occurrences (all)	1	14	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	11 / 57 (19.30%)	
occurrences (all)	0	12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	6 / 57 (10.53%)	
occurrences (all)	0	6	

Back pain			
subjects affected / exposed	1 / 6 (16.67%)	16 / 57 (28.07%)	
occurrences (all)	1	17	
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	4	
Groin pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Joint effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Joint range of motion decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 57 (8.77%)	
occurrences (all)	0	6	
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Osteopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	14 / 57 (24.56%)	
occurrences (all)	2	21	
Trismus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Infections and infestations			
Folliculitis			

subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Otitis media acute			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	5	
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 6 (50.00%)	22 / 57 (38.60%)	
occurrences (all)	3	23	
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	

Hyperkalaemia			
subjects affected / exposed	2 / 6 (33.33%)	3 / 57 (5.26%)	
occurrences (all)	2	3	
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Hypoalbuminaemia			
subjects affected / exposed	2 / 6 (33.33%)	7 / 57 (12.28%)	
occurrences (all)	2	7	
Hypocalcaemia			
subjects affected / exposed	1 / 6 (16.67%)	6 / 57 (10.53%)	
occurrences (all)	1	7	
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Hypomagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 57 (5.26%)	
occurrences (all)	1	3	
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	6 / 57 (10.53%)	
occurrences (all)	0	8	
Hypophosphataemia			
subjects affected / exposed	1 / 6 (16.67%)	4 / 57 (7.02%)	
occurrences (all)	2	6	
Vitamin D deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2013	Amendment 01: Administrative change for Medical Monitor and correct IND no.
01 May 2014	Amendment 02: • Starting dose and dosing in first 6 subjects with oral suspension of powder formulation; extended PK and evaluated DLT. • Minimum BSA required when pazopanib was tablet formulation. • Removed biomarker sample from hepatoblastoma cohort. • Added pregnancy monitoring.
15 February 2016	Amendment 03: • Clarification of monitoring for safety when pazopanib was powder suspension formulation. • Added new (re)screening process. • Clarification of enrollment process into 7 different cohorts. • Clarification of some inclusion (e.g. relapsed/refractory, bone marrow, thyroid) and exclusion (history of clinically significant bleeding) criteria. • Updated contraception and pregnancy information. • Clarification of dose reduction, interruption, and missed dose with pazopanib. • Clarification of TDM and study visit schedule. • Added new supportive care with blood-products. • Clarification of discontinuation of study treatment. • Clarification of end-of-study definition. • Added OS as new secondary efficacy objective. • Clarification of PK and exploratory correlative biology study. • Clarification of DLT and management of toxicities. • Clarification of statistical
02 May 2016	Amendment 04: • Administrative change to Novartis processes and Novartis procedures. • Removed any reference to GSK: Novartis and its authorized agents aligned with change and transfer of sponsorship. • New Novartis consent/assent form; GSK enrolled subjects were reconsented with Novartis.
23 May 2017	Amendment 05: • Any reconsented hepatotoxicity subjects: clarification of required approval from COG Study Chair before restart of treatment. • Updated contraception requirements for both male and female subjects. • Clarification/updated concomitant medications, prohibited medications, prior medications; removed exclusion criterion for 2 medications. • Clarification of end-of-study definition: option to close recruitment in a given cohort dependent upon efficacy response from 2 out of 3 primary cohorts at the end-of-stage 1 of the study. • Added DOR as new secondary efficacy objective. • Clarification that PK sampling was not required after Cycle 11. • Clarification regarding genotyping. • Clarification regarding data sets for efficacy analyses. Newly defined PP population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: